
Revised Clinical Study Protocol

Drug Substance	Tralokinumab (CAT-354)
Study Code	D2210C00007
Edition Number	3
Date	

A 52-Week, Multicentre, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tralokinumab in Adults and Adolescents with Asthma Inadequately Controlled on Inhaled Corticosteroid Plus Long-Acting β_2 -Agonist (STRATOS 1)

Sponsor: AstraZeneca

International Co-ordinating Investigator:

AstraZeneca Research and Development site representative

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1			
2			
3			
Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1			

PROTOCOL SYNOPSIS

A 52-Week, Multicentre, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tralokinumab in Adults and Adolescents with Asthma Inadequately Controlled on Inhaled Corticosteroid Plus Long-Acting β_2 -Agonist (STRATOS 1)

International Co-ordinating Investigator:

Study site(s) and number of subjects planned

Approximately 1140 subjects will be randomized at approximately 267 study sites worldwide.

Study period		Phase of development
Estimated date of first subject enrolled	Q2 2014	3
Estimated date of last subject completed	Q3 2017	3

Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of a fixed 300 mg dose of tralokinumab administered subcutaneously in subjects with uncontrolled asthma on inhaled corticosteroid plus long-acting β_2 -agonist and having a history of asthma exacerbations.

Approximately 1140 subjects will be randomized globally. Subjects will be stratified at randomization by serum periostin level (<16.44 ng/mL or ≥ 16.44 ng/mL) sampled during run-in, geographical region, and age group (adults versus adolescents).

Subjects will receive either of the following regimens of tralokinumab, or placebo, administered via subcutaneous injection to subjects at the study site, over a 52-week treatment period:

- Tralokinumab 300 mg, or placebo, every 2 weeks or,
- Tralokinumab 300 mg, or placebo, every 4 weeks

After initial enrolment and confirmation of entry criteria, subjects will proceed to a run-in period of 4 to 6 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Subjects who meet the eligibility criteria will be randomized to a 52-week treatment period.

Subjects will be maintained on their currently prescribed inhaled corticosteroid plus long-acting β_2 -agonist and any additional asthma controller medication, without change, from enrolment throughout the run-in and treatment period.

Follow-up visits will be conducted at Weeks 56 and 72. The extended follow-up period is to ensure that adequate determination of immunogenicity can be determined.

Objectives

Primary Objective:	Outcome Measures:
To evaluate the effect of tralokinumab 300 mg administered every 2 weeks compared with placebo on the annualised asthma exacerbation rate in adult and adolescent subjects with asthma that is inadequately controlled with inhaled corticosteroid plus long-acting β_2 -agonist	<p>Primary outcome variable: The annualised asthma exacerbation rate up to Week 52</p> <p>Primary outcome measure: Asthma exacerbation rate reduction</p> <p>An asthma exacerbation is defined by a worsening of asthma requiring:</p> <ul style="list-style-type: none"> • Use of systemic corticosteroids for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids • An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency room or urgent care center) due to asthma that required systemic corticosteroids (as per the above) • An inpatient hospitalization due to asthma (defined as an admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours)

Key Secondary Objectives:	Outcome Measures:
---------------------------	-------------------

<p>To evaluate the effect of tralokinumab 300 mg administered every 4 weeks compared with placebo on the annualised asthma exacerbation rate in adult and adolescent subjects with asthma that is inadequately controlled with inhaled corticosteroid plus long-acting β_2-agonist</p>	<p>Primary outcome variable: The annualised asthma exacerbation rate up to Week 52</p> <p>Primary outcome measure: Asthma exacerbation rate reduction</p> <p>An asthma exacerbation is defined by a worsening of asthma requiring:</p> <ul style="list-style-type: none"> • Use of systemic corticosteroids for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids • An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency room or urgent care center) due to asthma that required systemic corticosteroids (as per the above) • An inpatient hospitalization due to asthma (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours)
<p>To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to lung function</p>	<p>Key outcome variable: Percent change from baseline in pre-dose/pre-bronchodilator forced expiratory volume in 1 second</p> <p>Key outcome measure: Percent difference vs. placebo at Week 52</p>
<p>To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to asthma symptoms</p>	<p>Key outcome variable: Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary).</p> <p>Key outcome measure: Mean difference vs. placebo at Week 52</p>
<p>To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to asthma specific health-related quality of life</p>	<p>Key outcome variable: Change from baseline in Standardised Asthma Quality of Life Questionnaire for 12 Years and Older total score</p> <p>Key outcome measure: Mean difference vs. placebo at Week 52</p>

To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to Asthma Control Questionnaire-6 defined asthma control	<p>Key outcome variable: Change from baseline in Asthma Control Questionnaire-6</p> <p>Key outcome measure: Mean difference vs. placebo at Week 52</p>
---	--

Other Secondary Objectives:	Outcome Measures:
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to other endpoints associated with asthma exacerbations	<ul style="list-style-type: none"> Time to first asthma exacerbation and proportion of subjects with ≥ 1 asthma exacerbation
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to emergency room and urgent care visits and hospitalizations due to asthma	<ul style="list-style-type: none"> Annualised asthma exacerbation rate that is associated with an emergency room or urgent care visit, or a hospitalization
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards pre-dose and post bronchodilator forced expiratory volume in 1 second	<ul style="list-style-type: none"> Pre-dose/post-bronchodilator forced expiratory volume in 1 second
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to health related quality of life.	<ul style="list-style-type: none"> European Quality of Life - 5 Dimension 5 Level Daily Living Questionnaire
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to health care resource utilization and productivity loss due to asthma	<ul style="list-style-type: none"> Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire Asthma specific resource utilization (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications)
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to other measurements of asthma symptoms and asthma control	<ul style="list-style-type: none"> Rescue medication use Home peak expiratory flow (morning and evening) Night-time awakening due to asthma

To evaluate the pharmacokinetics and immunogenicity of 2 dosing regimens of tralokinumab	<ul style="list-style-type: none"> • Pharmacokinetic parameters: C_{trough} at steady-state • Immunogenicity outcome variables: incidence rate of positive anti-drug antibodies and characterization of their neutralizing potential
To identify a biomarker positive population based on periostin or dipeptidyl peptidase-4 baseline values that may be associated with up-regulation of interleukin-13	<p>Key outcome variable:</p> <ul style="list-style-type: none"> • The annualised asthma exacerbation rate up to Week 52 (key variable) <p>Other outcome variables:</p> <ul style="list-style-type: none"> • Percent change from baseline in pre-dose/pre-bronchodilator forced expiratory volume in 1 second • Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary) • Change from baseline in Standardised Asthma Quality of Life Questionnaire for 12 Years and Older • Change from baseline in Asthma Control Questionnaire-6

Safety Objectives:	Outcome Measures:
To evaluate the safety and tolerability of 2 dosing regimens of tralokinumab	<ul style="list-style-type: none"> • Adverse Events/Serious Adverse Events • Vital signs • Digital electrocardiograms • Clinical chemistry/haematology/urinalysis • Physical examinations

Exploratory Objectives:	Outcome Measures:
--------------------------------	--------------------------

<p>To explore baseline periostin, dipeptidyl peptidase-4, and other biomarkers that may be associated with up-regulation of interleukin-13, as predictive biomarker for treatment of 2 dosing regimens of tralokinumab</p>	<p>Key outcome variable:</p> <ul style="list-style-type: none"> • The annualised asthma exacerbation rate up to Week 52 (key variable) <p>Other outcome variables:</p> <ul style="list-style-type: none"> • Percent change from baseline in pre-dose/pre-bronchodilator forced expiratory volume in 1 second • Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary) • Change from baseline in Standardised Asthma Quality of Life Questionnaire for 12 Years and Older • Change from baseline in Asthma Control Questionnaire-6
<p>To explore change from baseline of biomarkers that may be associated with up-regulation of interleukin-13, and possible correlation with clinical efficacy of tralokinumab</p>	<p>Biomarkers will include:</p> <ul style="list-style-type: none"> • Blood eosinophils • Dipeptidyl peptidase-4 • Fractional exhaled nitric oxide • Periostin • Total serum Immunoglobulin E <p>Other biomarkers may be considered.</p>

<p>To evaluate the onset and maintenance of treatment effect with regards to lung function, symptoms, quality of life and global response of 2 dosing regimens of tralokinumab</p>	<ul style="list-style-type: none"> • Percent and absolute change from baseline in pre-dose/pre bronchodilator forced expiratory volume in 1 second • Change from baseline in mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary) • Change from baseline in Standardised Asthma Quality of Life Questionnaire for 12 Years and Older score • Percent change from baseline in Forced Vital Capacity and Forced Expiratory Flow 25-75% • Clinician - Global Impression of Change (CGIC) from baseline
<p>To collect and store deoxyribonucleic acid for future exploratory research into genes/genetic variation that may influence clinical response to tralokinumab and provide information on phenotypes of severe asthma (optional)</p>	<ul style="list-style-type: none"> • Deoxyribonucleic acid

Results from the exploratory analyses, if performed, may be reported separately from the Clinical Study Report.

Target subject population

Male and female adults and adolescents, 12-75 years of age inclusive, with asthma inadequately controlled by treatment with inhaled corticosteroid plus long-acting β_2 -agonist.

Duration of treatment

Following an initial enrolment at Week -4 to -6, subjects will enter a 4 to 6-week run-in period which will be followed by a 52-week treatment period. The first dose of tralokinumab/placebo will be administered at Week 0. For subjects receiving the bi-weekly treatment regimen, subsequent doses will be administered every 2 weeks up until Week 50 (for a total of 26 doses) with an end of treatment visit occurring at Week 52. For subjects receiving the treatment regimen every 4 weeks, subsequent doses will be administered every 4 weeks up until Week 48 (for a total of 13 doses) with an end of treatment visit occurring at Week 52. For both dosing regimen, investigational product (IP) cannot be administered within 7 days from the last dosing visit. Post-treatment safety follow up visits will be performed at Weeks 56 and 72.

Investigational product, dosage and mode of administration

Tralokinumab 300 mg (150 mg/mL), or placebo, will be administered to subjects via subcutaneous injection using 2 pre-filled syringes at the study site.

Statistical methods

The primary analysis of the efficacy endpoints will include all data captured during the double blind treatment period. The statistical analyses will compare both dosing regimens of tralokinumab to placebo. Efficacy and safety comparisons of tralokinumab versus placebo will be done using the pooled placebo cohorts, if not otherwise specified.

A hierarchical testing strategy will be applied for the confirmatory testing of primary and key secondary endpoints in the two dosing regimens to allow for control of type I error.

The primary efficacy objective will be evaluated through the null hypothesis test H_0 : rate ratio (tralokinumab/placebo) equals 1 vs. H_1 : rate ratio not equals 1. The test will be based on a negative binomial model. Covariates and factors included in the model will include at least treatment group and stratifying variables.

Key secondary outcome variables will be analyzed using a repeated measures analysis approach including at least treatment and stratifying variables as the explanatory variables.

A total of 1,140 subjects (380 per treatment group) are considered sufficient to show a reduction in annualised asthma exacerbation rate for tralokinumab compared to placebo in the overall study population.

The sample size calculations are based on an assumed annual exacerbation rate in the placebo group of 0.8 and shape parameter of 0.95 (over-dispersion). The methodology used is described in [Keene et al 2007](#). A power of at least 90% using a two-sided test at 5% significance level is required for the primary objective.

Assuming a uniform loss to follow-up of 15% during the study, 1,140 randomized subjects are expected to provide approximately 350 subject years at risk per treatment group. This is expected to provide at least 90% power for showing superiority with effects of down to 32% asthma exacerbation reduction rate in the all-comer population.

All safety parameters will be analyzed descriptively. The safety analyses will be based on the safety analysis data set, defined as all subjects who received at least 1 dose of investigational product.

	PAGE
PROTOCOL SYNOPSIS.....	2
TABLE OF CONTENTS.....	10
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	17
1. INTRODUCTION	21
1.1 Background and rationale for conducting this study	21
1.2 Rationale for study design, doses and control groups.....	22
1.3 Benefit/risk and ethical assessment.....	23
1.4 Study Design	24
2. STUDY OBJECTIVES.....	27
2.1 Primary objective	27
2.2 Secondary objectives	28
2.3 Safety objectives	30
2.4 Exploratory objectives	31
3. SUBJECT SELECTION, ENROLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL.....	32
3.1 Inclusion criteria	32
3.2 Exclusion criteria	36
3.3 Subject enrolment and randomization	39
3.4 Procedures for handling incorrectly enrolled or randomized subjects.....	39
3.5 Methods for assigning treatment groups.....	40
3.6 Methods for ensuring blinding.....	40
3.7 Methods for unblinding.....	41
3.8 Restrictions during and after the study	41
3.9 Discontinuation of investigational product.....	42
3.9.1 Procedures for discontinuation of a subject from investigational product	42
3.10 Criteria for withdrawal.....	43
3.10.1 Screen failures.....	43
3.10.2 Withdrawal of the informed consent or assent.....	43
4. STUDY PLAN AND TIMING OF PROCEDURES.....	45

4.1	Enrolment/run-in period.....	53
4.1.1	Enrolment (Visit 1)	53
4.1.2	Run-in (Visit 2).....	53
4.1.3	Randomization (Visit 3).....	54
4.1.4	Re-screening	54
4.2	Treatment period.....	55
4.3	Follow-up period.....	57
5.	STUDY ASSESSMENTS	57
5.1	Efficacy assessments.....	58
5.1.1	Assessment of asthma exacerbations	58
5.1.2	Spirometry.....	59
5.1.2.1	Reversibility test and post-BD FEV ₁ efficacy assessment	62
5.1.3	Home PEF testing	63
5.1.4	Periostin	64
5.1.5	Level of fractional exhaled nitric oxide	64
5.1.6	Safety assessments	65
5.1.6.1	Laboratory safety assessments	65
5.1.6.2	Pregnancy Test.....	70
5.1.7	Physical examination	70
5.1.7.1	Complete physical examination.....	70
5.1.7.2	Brief physical examination	70
5.1.8	dECG.....	70
5.1.8.1	Resting 12-lead dECG	71
5.1.9	Vital signs	71
5.1.9.1	Pulse, blood pressure and respiration rate.....	71
5.1.9.2	Body temperature.....	71
5.1.10	Other safety assessments.....	72
5.1.10.1	Serology	72
5.1.10.2	Infections.....	72
5.2	Other assessments	72
5.2.1	Weight and height	72
5.2.2	Patient reported outcomes.....	72
5.2.2.1	Asthma Daily Diary	73
5.2.2.2	Asthma Control Questionnaire (ACQ-6)	74
5.2.2.3	Standardised Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12).....	74
5.2.2.4	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ)	75
5.2.2.5	European quality of life-5 dimensions-5 levels (EQ-5D-5L)	75
5.2.2.6	Health care resource utilization.....	76
5.2.2.7	Clinician – Global Impression of Change (CGIC) assessment.....	76
5.3	Pharmacokinetics and Immunogenicity	76
5.3.1	Collection of samples.....	76

5.3.2	Determination of drug concentration	76
5.3.3	Storage and destruction of pharmacokinetic samples	77
5.3.4	Immunogenicity	77
5.3.5	Total IgE	78
5.3.6	Phadiatop.....	78
5.4	Pharmacodynamics	78
5.4.1	Serum biomarkers	78
5.5	Pharmacogenetics	78
5.5.1	Collection of pharmacogenetic samples (optional).....	78
5.5.2	Storage, re-use and destruction of pharmacogenetic samples	79
5.6	Biomarker analysis.....	79
5.6.1	Storage, re-use and destruction of biological samples	79
5.6.2	Labelling and shipment of biological samples.....	80
5.6.3	Chain of custody of biological samples	80
5.6.4	Withdrawal of Informed Consent or Assent for donated biological samples	80
6.	SAFETY REPORTING AND MEDICAL MANAGEMENT	81
6.1	Definition of adverse events	81
6.2	Definitions of serious adverse event	81
6.3	Recording of adverse events	82
6.3.1	Time period for collection of adverse events.....	82
6.3.2	Follow-up of unresolved adverse events.....	82
6.3.3	Adverse event variables	82
6.3.4	Assessment of causality	83
6.3.5	Adverse events based on signs and symptoms.....	83
6.3.6	Adverse events based on examinations and tests.....	83
6.3.7	Hy's Law.....	84
6.3.8	Disease progression	84
6.4	Reporting of serious adverse events.....	84
6.5	Overdose	85
6.6	Pregnancy.....	86
6.6.1	Maternal exposure.....	86
6.6.2	Paternal exposure	86
6.7	Management of IP related toxicities	86
6.8	Study governance and oversight	87
6.8.1	Independent Adjudication Committee	87
6.8.2	Data and safety monitoring board.....	87
7.	INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS	88
7.1	Identity of investigational product(s).....	88
7.2	Dose and treatment regimens.....	89

7.3	Labelling	90
7.4	Storage	90
7.5	Compliance	91
7.6	Accountability	91
7.7	Concomitant and other treatments	91
7.7.1	Concomitant medications	91
7.7.2	Restrictions during and after the study	92
7.7.2.1	Asthma medication restrictions	92
7.7.2.2	Other medication restrictions	94
7.7.2.3	Bronchial thermoplasty	95
7.7.3	Other treatments	95
8.	STATISTICAL ANALYSES BY ASTRAZENECA	95
8.1	Statistical considerations	95
8.2	Sample size estimate	96
8.3	Definitions of analysis sets	96
8.3.1	Efficacy analysis set	96
8.3.2	Safety analysis set	96
8.3.3	PK analysis set	97
8.3.4	PRO analysis set	97
8.4	Outcome measures for analyses	97
8.4.1	General Definitions	97
8.4.1.1	Definition of baseline and subject baseline variables	97
8.4.1.2	Visit and period windows	97
8.4.2	Calculation or derivation of efficacy variables	98
8.4.2.1	Exacerbation rate	98
8.4.2.2	Proportion of subjects with ≥ 1 asthma exacerbation during 52 weeks of treatment	99
8.4.2.3	Time to first exacerbation	99
8.4.2.4	Forced expiratory volume in 1 second	99
8.4.2.5	Forced Vital Capacity and Forced Expiratory Flow at 25-75%	99
8.4.2.6	Annualised asthma exacerbation rate associated with an ER or urgent care visit or a hospitalization	99
8.4.3	Calculation or derivation of patient reported outcome variables	100
8.4.3.1	Asthma symptom score	100
8.4.3.2	Rescue medication use	100
8.4.3.3	Home peak expiratory flow (morning and evening)	101
8.4.3.4	Asthma Control Questionnaire (ACQ-6)	101
8.4.3.5	Asthma quality of life questionnaire for 12 years and older (AQLQ(S)+12)	102
8.4.3.6	European quality of life-5 dimensions-5 levels (EQ-5D-5L)	102
8.4.3.7	Health care resource utilization	103

8.4.3.8	The Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ).....	103
8.4.4	Calculation or derivation of safety variable(s).....	104
8.4.4.1	Adverse events	104
8.4.4.2	Other significant adverse events	105
8.4.4.3	Laboratory variables	105
8.4.4.4	dECGs	106
8.4.4.5	Physical examination	106
8.4.4.6	Vital signs	106
8.4.5	Calculations or derivation of Pharmacokinetic and Immunogenicity variables	107
8.5	Methods for statistical analyses	107
8.5.1	Testing strategy for primary and key secondary objectives.....	108
8.5.2	Sensitivity analyses	109
8.5.3	Subject disposition, demography data and subjects characteristics	109
8.5.4	Exposure	110
8.5.5	Violations and deviations.....	110
8.5.6	Analysis of the primary variable.....	111
8.5.7	Analysis of secondary variable(s)	111
8.5.7.1	Lung Function.....	111
8.5.7.2	Asthma symptoms.....	112
8.5.7.3	Asthma specific health-related quality of life	112
8.5.7.4	ACQ-6 defined asthma control	112
8.5.7.5	Biomarker positive population based on subject's baseline periostin or baseline DPP4 values	113
8.5.7.6	Other endpoints associated with asthma exacerbations	114
8.5.7.7	Emergency room or urgent care visits and hospitalizations due to asthma	115
8.5.7.8	Health care resource utilization and productivity loss due to asthma.....	115
8.5.7.9	Asthma symptom, general health-related quality of life and asthma control	115
8.5.8	Safety and tolerability	116
8.5.8.1	Adverse events	116
8.5.8.2	Laboratory data	116
8.5.8.3	dECGs	117
8.5.8.4	Physical Examination.....	118
8.5.8.5	Vital Signs.....	118
8.5.8.6	Analysis of Immunogenicity variables	118
8.5.9	Analysis of pharmacokinetics	118
8.5.10	Interim analysis	119
8.5.11	Exploratory analysis.....	119
8.5.11.1	Baseline periostin and DPP4 levels as predictive biomarkers	119
8.5.11.2	Deoxyribonucleic acid collected for future exploratory research.....	119
9.	STUDY AND DATA MANAGEMENT BY ASTRAZENECA	119
9.1	Training of study site personnel.....	119
9.2	Monitoring of the study	120

9.2.1	Source data	120
9.2.2	Study agreements	120
9.2.3	Archiving of study documents	120
9.3	Study timetable and end of study	120
9.4	Data management by AstraZeneca	121
10.	ETHICAL AND REGULATORY REQUIREMENTS	122
10.1	Ethical conduct of the study	122
10.2	Subject data protection	122
10.2.1	Pharmacogenomic data	122
10.3	Ethics and regulatory review	123
10.4	Informed consent and assent	123
10.5	Changes to the protocol and informed consent or assent forms	124
10.6	Audits and inspections	124
11.	LIST OF REFERENCES	125

LIST OF TABLES

Table 1	Study Plan	45
Table 2	List of safety laboratory tests	65
Table 3	Clinical chemistry tests schedule	66
Table 4	Haematology/Haemostasis (whole blood) schedule	67
Table 5	Urinalysis schedule	68
Table 6	Volume of blood to be drawn from each subject	69
Table 7	Identity of investigational product	88

LIST OF FIGURES

Figure 1	Study flow chart	26
Figure 2	Injection sites and rotation scheme	89

LIST OF APPENDICES

Appendix A	Signatures
Appendix B	Additional Safety Information
Appendix C	IATA 6.2 Guidance document
Appendix D	Pharmacogenetics Research
Appendix E	Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law
Appendix F	Maintenance Therapy Equivalence Table
Appendix G	Anaphylaxis: definition, signs and symptoms, management
Appendix H	Restricted and prohibited medications

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-Drug Antibodies
AE	Adverse Event
AAER	Annual Asthma Exacerbation Rate
AERR	Asthma Exacerbation Reduction Rate
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APFS	Accessorized Pre-filled Syringe
AQLQ(S)+12	Standardised Asthma Quality of Life Questionnaire for 12 Years and Older
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society/European Respiratory Society
BD	Bronchodilator
β-HCG	Beta-Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
CGIC	Clinical – Global Impression of Change
CO ₂	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CSA	Clinical Study Agreement
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
dECG	Digital Electrocardiogram
DNA	Deoxyribonucleic Acid
DPP4	Dipeptidyl Peptidase-4
DSMB	Data and Safety Monitoring Board

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	Electronic Case Report Form
ER	Emergency Room
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome device
EQ-5D-5L	European Quality of Life - 5 Dimensions 5 Level
FEF 25-75%	Forced Expiratory Flow at 25-75% of the forced vital capacity
FE _{NO}	Fractional Exhaled Nitric Oxide
FEV ₁	Forced Expiratory Volume in 1 second
FSH	Follicle-Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GINA	Global Initiative for Asthma
GLI	The Global Lung Function Initiative
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
ICI	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
IL-13	Interleukin-13
IP	Investigational Product
IPD	Investigational Product Discontinuation
IRB	Institutional Review Board

Abbreviation or special term	Explanation
ISF	Investigator Study File
ITT	Intent-to-Treat
IUO	Investigational Use Only
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-Acting β_2 -Agonist
LTRA	Leukotriene Receptor Antagonists
MAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
nAB	Neutralizing Antibodies
OCS	Oral Corticosteroids
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PEO	Performance Evaluation Only
PK	Pharmacokinetic(s)
PNV	Predicted Normal Value
PRO	Patient Reported Outcome
PT	Preferred Term
Q2W	Every 2 Weeks
Q4W	Every 4 Weeks
SABA	Short-Acting β_2 -Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System Organ Class
Th2	T Helper 2 Cells
TLC	Total Lung Capacity
ULN	Upper Limit of Normal
UNS	Unscheduled

Abbreviation or special term	Explanation
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Asthma is a syndrome characterized by airway inflammation, reversible airway obstruction and airway hyperresponsiveness, with a global prevalence of approximately 300 million patients ([GINA 2012](#)).

Approximately 5% to 10% of asthma patients have severe asthma, many of whom may be inadequately controlled by inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABA) in combination with additional controller therapies ([Bateman et al 2010](#)). These patients are at risk of asthma exacerbations, have a large medical need, and represent the greatest economic burden ([Accordini et al 2006](#)).

The observed variability in clinical response to currently available asthma therapies appears to be related, in part, to distinctive inflammatory phenotypes ([Wenzel 2012](#)). There is considerable evidence that interleukin-13 (IL-13) is a key mediator in the pathogenesis of asthmatic disease. IL-13 is secreted predominantly by CD4+ T-helper 2 (Th2) cells and IL-13 receptors are expressed on a number of cell types including those involved in the pathogenesis of asthma ([Hershey 2003](#)). There is evidence to support that IL-13 can increase development of airway hyperresponsiveness ([Wardlaw et al 1988](#)), potentiate bronchoconstriction ([Grunstein et al 2002](#)), increase the number of mucus-secreting cells and promote airway fibrosis in asthma ([Wills-Karp et al 1998](#)).

Tralokinumab is a human recombinant monoclonal antibody (MAb) of the immunoglobulin G4 subclass that specifically binds human IL-13, blocking interactions with the IL-13 receptor. Tralokinumab is in development for the treatment of severe asthma. A phase 2a study (MI-CP199) provided evidence of improvement of lung function (forced expiratory volume in 1 second (FEV₁)), following the addition of subcutaneous (SC) tralokinumab to standard asthma controller medications. Doses of 300 and 600 mg every 2 weeks of tralokinumab both resulted in comparable effects in FEV₁ that were greater than that observed with a 150 mg dose ([Piper et al 2013](#)). Since low pre-bronchodilator (BD) FEV₁ has been identified as a strong independent predictor of subsequent asthma exacerbations, it is plausible that the addition of tralokinumab will reduce the rate of asthma exacerbations in this population ([Reddel et al 2009](#)).

In a phase 2b (CD-RI-CAT-354-1049) study with tralokinumab in adults with uncontrolled, severe asthma requiring high dose ICS and LABA, the efficacy and safety of the 2 regimens (300 mg every 2 weeks (Q2W) or, 300 mg Q2W for 12 weeks, followed by a 300 mg every 4 weeks (Q4W) maintenance dosing [Q2/4W]) vs. placebo, was evaluated over a treatment period of 52 weeks. The primary endpoint for this study was the annualised asthma exacerbation rate (AAER) over 52 weeks, with secondary endpoints including pulmonary function, patient reported outcomes, including asthma symptoms. In the overall intent-to-treat (ITT) phase 2b population, an increase from baseline in pre-BD FEV₁ to the end of treatment was seen with the Q2W dosing regime, but not with the Q2/4W dosing regime.

In this phase 2b study, a subpopulation reversible on entry (FEV_1 reversibility $\geq 12\%$ and ≥ 200 ml in FEV_1) an AAER reduction that was greater for the tralokinumab 300 mg Q2W cohort versus the Q2/4W cohort was seen. A further reduction of AAER was observed in a subgroup of reversible subjects with - ($>$ median) serum periostin, a biomarker induced by IL-13. This is the population to be studied in phase 3. The safety profile of all doses studied so far has been acceptable (for further details see the investigators brochure (IB)).

The purpose of this phase 3 study is to provide confirmatory evidence of the efficacy and safety of tralokinumab in the treatment of subjects with severe uncontrolled asthma despite treatment with ICS-LABA and any other additional controller medication. The study will evaluate the AAER and other aspects of lung function, asthma control, and safety to further characterize the benefit-risk profile of the drug and understand how best to position it in the treatment pathway. The study will also address the potential identification of a target population with an enhanced response rate based on the presence of high serum periostin as an indicator of IL-13 driven asthma. Periostin levels will be determined in this study using an investigational use only (IUO)/performance evaluation only (PEO) assay being specifically developed and validated as a companion diagnostic for tralokinumab. The utility of alternative biomarkers, such as dipeptidyl peptidase-4 (DPP4), for determining efficacy will also be investigated.

1.2 Rationale for study design, doses and control groups

This is a global study designed to investigate the safety and efficacy of the fixed dose Tralokinumab (300mg) administered via SC injection every 2 or 4 weeks throughout a 52-week treatment period as follows:

- Tralokinumab 300 mg, or placebo, Q2W (26 doses) or,
- Tralokinumab 300 mg, or placebo, Q4W (13 doses)

Exacerbation-prone asthma subjects who remain uncontrolled on ICS-LABA, and who demonstrate a reversibility $\geq 12\%$ and ≥ 200 mL in FEV_1 at either visit 2 (run-in) or Visit 3 (randomization), will be randomized into the study. Primary efficacy will be determined based on reduction in the rate of asthma exacerbations over 52 weeks for tralokinumab versus placebo. Subjects will be stratified at randomization by serum periostin level (<16.44 ng/mL or ≥ 16.44 ng/mL) sampled during run-in, geographical region, and age group (adults versus adolescents).

Previous efficacy studies of tralokinumab, including a phase 2b study with subjects on high dose ICS-LABA with or without additional asthma controller medications, have been conducted in adult subjects (18-75 years of age), and provide the basis for this pivotal phase 3 study. Pharmacokinetic evaluations in adolescents with asthma confirm that the same dose as for adults is applicable and since it is expected that adolescent subjects (12-17 years of age) will respond similarly to adults, and are therefore to be included as part of the study population. Adolescents will therefore be recruited in the pivotal phase 3 studies.

Analysis of data from both phase 2 studies MI-CP199 and the phase 2b study, has demonstrated a clinically relevant effect on FEV₁ from tralokinumab 300 mg Q2W. In contrast, only limited, if any, improvement was observed with 150 mg Q2W (in study MI-CP199) or 300 mg Q2/4W (in study CD-RI-CAT-354-1049). Furthermore, an effect on AAER was observed with the 300 mg Q2W dosing regimen, but not with the Q2/4W dosing regimen in study CD-RI-CAT-354-1049. Since the safety profile in the CD-RI-CAT-354-1049 study was acceptable in both treatment cohorts, and no clear safety related dose-response pattern was identified, the doses of 300 mg Q2W, and 300 mg Q4W, have been selected for evaluation in this phase 3 study. The 300 mg Q4W dosing regimen has been selected to characterize the dose response in the target phase III population.

Pharmacokinetic/pharmacodynamic (PK/PD) modelling using all data obtained to date has also confirmed that a dose of 300 mg Q2W will result in near maximal increase in pre-BD FEV₁ in the phase 3 subject population.

Subjects on placebo will receive maintenance therapy that includes their usual dose of ICS/LABA (see section 7.7.2).

1.3 Benefit/risk and ethical assessment

There are few treatment options for subjects whose asthma remains uncontrolled on ICS-LABA (GINA 2012). The evidence base for oral add-on therapies (i.e. oral corticosteroids (OCS), leukotriene inhibitors (LTRAs), and xanthenes) is limited. Anti-immunoglobulin E (IgE) therapy (i.e., omalizumab) improves control in a subset of subjects with severe asthma associated with IgE-mediated allergy to a perennial allergen. Hence, new therapies are needed for asthma management in subjects who remain uncontrolled on standard of care.

IL-13 is targeted as it plays a role in the allergic/Th2 type response which is a signature of asthma. An anti-IL-13 treatment may therefore be useful in treatment of asthma. Data from phase 2 studies support this notion. Thus, in a 24 week phase 2a study (MI-CP199) tralokinumab at a dose of 300 mg SC every 2 weeks (the dose proposed for the phase 3 programme) provided improvement of lung function (FEV₁), when added to standard asthma controller medications. In addition the efficacy of tralokinumab has been studied in a 1 year long phase 2b study (CD-RI-CAT-354-1049) targeting adult subjects whose asthma was poorly controlled by high dose ICS-LABA. In this study, tralokinumab at a fixed dose of \geq 300 mg SC every other week produced improvements in multiple metrics of asthma control, including the annualised asthma exacerbation rate (AAER), lung function, Asthma Control Questionnaire-6 (ACQ-6) scores, and symptoms, in a subpopulation who demonstrated reversibility of FEV₁ upon study entry.

Approximately 520 subjects with asthma have so far been exposed to tralokinumab at various doses and for different periods of time. The 1 year long phase 2b study has contributed 301 of these subjects with 140 of them receiving 300 mg every other week. In all studies conducted so far, tralokinumab has been well tolerated, and no safety concerns have been identified.

However, because it is believed that the Th2 response may be of importance in the defense against helminthic parasitic infections, a theoretical risk for such infestations exists. IL-13 may also play a role in regulating tumours (Hallett et al 2012), and although evidence for this is scarce and inconclusive, this theoretical risk needs to be considered. In conjunction with the performance of routine pharmacovigilance activities risk minimization measures therefore include exclusion of subjects with untreated parasitic infection and active or recent malignancy.

As with all biologics therapies, anti-drug antibodies (ADA), including neutralizing antibodies (nAb), may develop. Development of ADA to tralokinumab has been rare in the phase 1 and 2 studies conducted thus far (<1% overall). Theoretical risks due to development of ADA include decreased drug efficacy and hypersensitivity reactions (e.g., anaphylaxis or immune complex disease) and observation following administration of tralokinumab is therefore mandated.

Pharmacokinetic modelling suggests that exposure to tralokinumab is slightly higher in adolescents (12-17 years of age) than that in adults; however, considering the overall variability of tralokinumab PK, and the absence of safety findings at doses at or above than 300 mg every other week in the phase 2 studies, dose adjustment is not considered to be required for subjects in this age group.

In summary, the efficacy and safety data obtained to date support the continued clinical development of tralokinumab in adult and adolescent subjects with uncontrolled asthma

A detailed assessment of the risk/benefit of tralokinumab in subjects with asthma is given in the IB.

1.4 Study Design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of a fixed 300 mg dose of tralokinumab administered SC in subjects with uncontrolled asthma receiving ICS ($\geq 500\mu\text{g}$ fluticasone propionate dry powder formulation equivalents total daily dose) and a LABA, and having a history of asthma exacerbations.

Two regimens of tralokinumab, or placebo, will be administered via SC injection to subjects at the study site over a 52 week treatment period as follows:

- Tralokinumab 300 mg, or placebo, Q2W (26 doses) or,
- Tralokinumab 300 mg, or placebo, Q4W (13 doses)

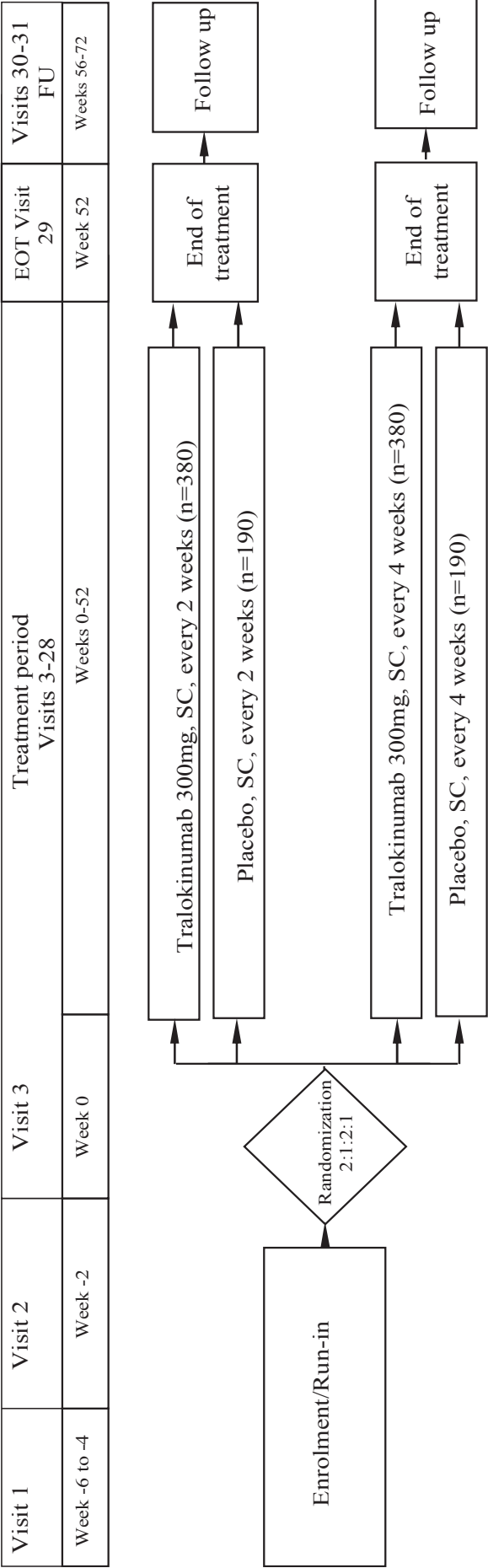
Approximately 1140 subjects will be randomized at approximately 305 sites globally. Subjects will be stratified at randomization by serum periostin level (<16.44 ng/mL or ≥ 16.44 ng/mL) sampled during run-in, geographical region, and age group (i.e. adults versus adolescents).

After initial enrolment and confirmation of entry criteria, subjects will enter a run-in period of 4 to 6 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Subjects who meet eligibility criteria will be randomized to a 52-week treatment period. The first dose of tralokinumab/placebo will be administered at Week 0. For subjects receiving the Q2W treatment regimen, subsequent doses will be administered every 2 weeks up until Week 50 (for a total of 26 doses) with an end of treatment (EOT) visit occurring at Week 52. For subjects receiving the Q4W treatment regimen, subsequent doses will be administered every 4 weeks up until Week 48 (for a total of 13 doses) with an EOT visit occurring at Week 52. Subjects will be maintained on their currently prescribed ICS-LABA and any additional maintenance asthma controller medications, without change, from enrolment throughout the run-in and treatment period. All subjects will have site visits every 2 weeks.

Follow-up visits will be conducted at Weeks 56 and 72. The extended follow-up period is to ensure that adequate determination of immunogenicity can be determined.

An independent Adjudication Committee, blinded to the treatment of the subjects, will evaluate cases of ER or urgent care visits and hospitalizations, as well as all deaths, to determine whether they are due to asthma or not. For completeness, the adjudication committee will also be tasked with reviewing cardiovascular, cerebrovascular and malignant adverse events occurring after randomization. An independent Data and Safety Monitoring Board (DSMB) will safeguard the interest of adolescent subjects by assessing the safety of the intervention.

Figure 1 Study flow chart



2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To evaluate the effect of tralokinumab 300 mg administered every 2 weeks compared with placebo on the annualised asthma exacerbation rate in adult and adolescent subjects with asthma that is inadequately controlled with inhaled corticosteroid plus long-acting β_2 -agonist	<p>Primary outcome variable: The annualised asthma exacerbation rate up to Week 52</p> <p>Primary outcome measure: Asthma exacerbation rate reduction (AERR)</p> <p>An asthma exacerbation is defined by a worsening of asthma requiring:</p> <ul style="list-style-type: none"> • Use of systemic corticosteroids for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids • An emergency room (ER) or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency room (ER) or urgent care center) due to asthma that required systemic corticosteroids (as per the above) • An inpatient hospitalization due to asthma (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours)

2.2 Secondary objectives

Key Secondary Objectives:	Outcome Measures:
<p>To evaluate the effect of tralokinumab 300 mg administered every 4 weeks compared with placebo on the annualised asthma exacerbation rate in adult and adolescent subjects with asthma that is inadequately controlled with inhaled corticosteroid plus long-acting β_2-agonist</p>	<p>Primary outcome variable: The annualised asthma exacerbation rate up to Week 52</p> <p>Primary outcome measure: Asthma exacerbation rate reduction</p> <p>An asthma exacerbation is defined by a worsening of asthma requiring:</p> <ul style="list-style-type: none"> • Use of systemic corticosteroids for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids • An emergency room (ER) or urgent care visit (defined as evaluation and treatment for <24 hours in an ER or urgent care center) due to asthma that required systemic corticosteroids (as per the above) • An inpatient hospitalization due to asthma (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours)
<p>To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to lung function.</p>	<p>Key outcome variable: Percent change from baseline in pre-dose/pre-BD FEV₁</p> <p>Key outcome measure: Percent difference vs. placebo at Week 52</p>
<p>To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to asthma symptoms.</p>	<p>Key outcome variable: Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary)</p> <p>Key outcome measure: Mean difference vs. placebo at Week 52</p>

To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to asthma specific health-related quality of life.	<p>Key outcome variable: Change from baseline in Standardised Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ (S) +12) total score</p> <p>Key outcome measure: Mean difference vs. placebo at Week 52</p>
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to ACQ-6 defined asthma control.	<p>Key outcome variable: Change from baseline in ACQ-6</p> <p>Key outcome measure: Mean difference vs. placebo at Week 52</p>

Other Secondary Objectives:	Outcome Measures:
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to other endpoints associated with asthma exacerbations.	<ul style="list-style-type: none"> Time to first asthma exacerbation and proportion of subjects with ≥ 1 asthma exacerbation
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to ER or urgent care visits and hospitalizations due to asthma.	<ul style="list-style-type: none"> Annualised asthma exacerbation rate (AAER) that is associated with an ER or urgent care visit, or a hospitalization
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards pre-dose and post BD FEV ₁	<ul style="list-style-type: none"> Pre-dose/post-BD FEV₁
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to health related quality of life.	<ul style="list-style-type: none"> EuroQoL 5 Dimension 5 Level (EQ-5D-5L) Daily Living Questionnaire
To assess the effect of 2 dosing regimens of tralokinumab compared with placebo in two subject populations with regards to health care resource utilization and productivity loss due to asthma.	<ul style="list-style-type: none"> Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire Asthma specific resource utilization (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications)

To assess the effect of 2 dosing regimens of tralokinumab compared with placebo with regards to other measurements of asthma symptoms and asthma control.	<ul style="list-style-type: none"> • Rescue medication use • Home peak expiratory flow (PEF) - morning and evening • Night-time awakening due to asthma
To evaluate the pharmacokinetics and immunogenicity of 2 dosing regimens of tralokinumab	<ul style="list-style-type: none"> • Pharmacokinetic parameters: C_{trough} at steady-state • Immunogenicity outcome variables: incidence rate of positive anti-drug antibodies and characterization of their neutralizing potential
To identify a biomarker positive population based on periostin or DPP4 baseline values that may be associated with up regulation of IL-13	<p>Key outcome variable:</p> <ul style="list-style-type: none"> • The annualised asthma exacerbation rate up to Week 52 (key variable) <p>Other outcome variables:</p> <ul style="list-style-type: none"> • Percent change from baseline in pre-dose/pre-BD FEV₁ • Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary) • Change from baseline in AQLQ (S) +12 • Change from baseline in ACQ-6

2.3 Safety objectives

Safety Objectives:	Outcome Measures:
To evaluate the safety and tolerability of 2 dosing regimens of tralokinumab.	<ul style="list-style-type: none"> • Adverse Events/Serious Adverse Events (AEs/SAEs) • Vital signs • Digital electrocardiograms (dECGs) • Clinical chemistry/haematology/urinalysis • Physical examinations

2.4 Exploratory objectives

Exploratory Objectives:	Outcome Measures:
<p>To explore baseline periostin, DDP4, and other biomarkers that may be associated with up regulation of IL-13, as predictive biomarker for treatment of 2 dosing regimens of tralokinumab</p>	<p>Key outcome variable:</p> <ul style="list-style-type: none"> • The annualised asthma exacerbation rate up to Week 52 (key variable) <p>Other outcome variables:</p> <ul style="list-style-type: none"> • Percent change from baseline in pre-dose/pre-BD FEV₁ • Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary) • Change from baseline in AQLQ (S) +12 • Change from baseline in ACQ-6
<p>To explore change from baseline of biomarkers that may be associated with up regulation of IL-13, and possible correlation with clinical efficacy of tralokinumab</p>	<p>Biomarkers will include:</p> <ul style="list-style-type: none"> • Blood eosinophils • DPP4 • FE_{NO} • Periostin • Total serum IgE <p>Other biomarkers may be considered.</p>
<p>To evaluate the onset and maintenance of treatment effect with regards to lung function, symptoms, quality of life and global response of 2 dosing regimens of tralokinumab</p>	<ul style="list-style-type: none"> • Percent and absolute change from baseline in pre-dose/pre BD FEV₁ • Change from baseline in mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary) • Change from baseline in AQLQ (S) +12 • Percent change from baseline in FVC and FEF 25-75% • Clinician - Global Impression of Change (CGIC) from baseline

To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence clinical response to tralokinumab and provide information on phenotypes of severe asthma (optional)	<ul style="list-style-type: none"> • DNA
--	---

Results from this exploratory work will be reported outside of the clinical study report (CSR).

3. SUBJECT SELECTION, ENROLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study, subjects should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures for subjects who are at, or over the age of majority (as per local law). For subjects less than the age of majority, in addition to the subject providing informed assent, the subject's legal guardian must also provide their informed consent.
2. Female and male aged from 12 to 75 years, inclusively at time of enrolment (Visit 1). For those countries where local regulations permit enrolment of adults only, subject recruitment will be restricted to those who are ≥ 18 years.
3. Women of childbearing potential (WOCBP) (after menarche), including adolescent females, must use a highly effective form of birth control (confirmed by the investigator). Highly effective forms of birth control includes: true sexual abstinence, a vasectomised sexual partner, Implanon, female sterilization by tubal occlusion, any effective intrauterine device/system (IUD/IUS), Depo-ProveraTM injections, oral contraceptive, and Evra PatchTM or NuvaringTM. WOCBP must agree to use highly effective method of birth control, as defined above, from enrolment, throughout the study duration and within 16 weeks after last dose of investigational product (IP), and have negative serum pregnancy test result at Visit 1.

Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.
 - Women ≥ 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.
4. Weight of ≥ 40 and < 150 kg at enrolment (Visit 1).
 5. Documented physician-diagnosed asthma for at least 12 months prior to enrolment with the subject having received an asthma controller regimen requiring treatment with medium-to-high dose ICS for at least 6 of the 12 months prior to enrolment (Visit 1). In addition, subjects must have used physician prescribed ICS (at a total daily dose $\geq 500\mu\text{g}$ fluticasone propionate via dry powder inhaler or equivalent delivered dose) that has been taken at a stable dose for at least 3 months prior to enrolment.
 6. Documented treatment with ICS at a total daily dose corresponding to $\geq 500\mu\text{g}$ fluticasone propionate dry powder formulation equivalents and a LABA for at least 3 months prior to Visit 1. The ICS and LABA can be parts of a combination product, or given by separate inhalers. For ICS-LABA combination preparations, the highest strength approved maintenance dose in the local country will be acceptable to meet this ICS criterion.
 - In order to aid the assessment, ICS equivalents for high-dose and moderate-dose fluticasone propionate dry powder, as published by the Global Initiative for Asthma ([GINA 2012](#)) guidelines, are presented in [Appendix F](#). The Investigator will assess the subject's total daily ICS dose and determine that it corresponds to $\geq 500\mu\text{g}$ fluticasone propionate dry powder formulation equivalents. If the subject is on two or more different types of ICS, these can form parts of an addition, and the sum, however approximate, will be assessed.

The below defines the minimally acceptable documentation for subject inclusion:

1. Signed and dated notes from a referring physician, including name and dose of the ICS-LABA inhaler (or names and dosages, if used as separate inhalers).
2. Evidence of prescriptions for ICS-LABA medications that demonstrate coverage for the duration specified in Inclusion criteria 6 and 7.
3. Documented communication (e.g. phone conversation) clarifying that the subject received treatment with ICS-LABA for asthma. The name, dosage,

and duration of use for each medication must be recorded. This option should be used only if reasonable attempts to procure subject records have been unsuccessful.

7. Additional maintenance asthma controller medications are allowed according to standard practice of care. These medications must be stable for 3 months prior to enrolment (Visit 1). Furthermore, after randomization, the subject's background maintenance medication for asthma shall remain unchanged throughout the study.
8. At Visit 1 the subject must have a morning pre-BD FEV₁ value <80% (<90% for subjects 12 to 17 years of age) of their predicted normal value (PNV). At Visit 2 the subject must have a morning pre-BD FEV₁ value of ≥ 40 and <80% value (<90% for subjects 12 to 17 years of age) of their PNV. If this is not met at Visit 2, it must be met at Visit 3. Prior to the lung function measurement, the subject should withhold their BD for the effect duration specific to that BD.
9. A post-BD reversibility of $\geq 12\%$ and ≥ 200 mL in FEV₁ at Visit 2. If not met at Visit 2, it must be met at Visit 3 (randomization). Before reversibility testing, the subject should withhold their BD for the effect duration specific to that BD.
10. At least 2 documented asthma exacerbations in the 12 months prior to the date informed consent is obtained that required use of a systemic corticosteroid. In case of subjects who are re-screened within 30 days of their screen failure date; the 12 months can be calculated from the date that the first informed consent was obtained.

The below defines what is acceptable to document exacerbations in this Program:

1. Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a subject was hospitalized/treated with systemic steroids for an asthma exacerbation.
2. Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic steroids.
3. Subjects can provide evidence of prescriptions for systemic steroids used during an exacerbation.
4. A documented conversation between the treating/referral physician or nurse/nurse practitioner certifying that a subject was treated for an exacerbation with steroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure patient records have been unsuccessful.

A combination of the above is acceptable to document the two required exacerbations. However, it is necessary for the Investigator to document how they obtained confirmation of the subject's asthma exacerbations. It is the Investigator's responsibility to ensure subject eligibility into the clinical study. In cases where the Investigator feels that alternative records to the above constitutes acceptable documentation, the Study Physician will be contacted for their assessment of eligibility **prior** to enrolment. Every attempt should be made to obtain appropriate source documentation of medical records.

11. ACQ-6 score ≥ 1.5 at Visit 1 (Week - 6)

Prior to randomization at Visit 3, subjects should fulfil the following inclusion criteria:

12. For WOCBP (including all adolescents) only: have a negative urine pregnancy test prior to administration of the IP.
13. No requirement for additional asthma controller medication including an increase in ICS dose during run-in.
14. Fulfilment of at least one of the following conditions over the 7 days prior to randomization:
- 2 days with a daytime or night-time symptoms score ≥ 1
 - Reliever SABA use on > 2 days
 - ≥ 1 awakening due to asthma
15. A morning pre-BD FEV1 of $\geq 40\%$ and $< 80\%$ ($< 90\%$ for subjects 12 to 17 years of age) of the subject's PNV at the day of the randomization visit, if not met at Visit 2.
16. If not previously achieved at Visit 2, a post-BD reversibility in FEV1 of $\geq 12\%$ and ≥ 200 mL must be met at Visit 3. Note that theophylline and BDs must be withheld prior to reversibility testing to avoid interference with this assessment; the minimum period for withholding each medication is specified in [Appendix H](#).
17. Ability to perform acceptable inhaler, peak flow meter, and spirometry techniques.
18. Show at least 70% compliance with both the usual asthma controller (i.e. ICS-LABA and any other asthma controller medications) as evidenced by the subject having a minimum of 10 fully compliant dosing days in the 14 days prior to Visit 3 (randomization) as reported by the subject in the eDiary.
19. Compliance with eDiary assessment schedule
- At least 10 of the 14 days prior to Visit 3 must have complete (morning and evening) eDiary assessments.

For inclusion in the voluntary pharmacogenetic research, subjects should fulfil the following criterion:

20. Provision of a signed and dated written informed consent for the pharmacogenetic sample and analysis. If a subject declines to participate in the pharmacogenetic research, there will be no consequence or loss of benefit to the subject. The subject will not be excluded from the other aspects of the study described in the CSP, as long as they consent to participate in the study.

3.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Clinically important pulmonary disease other than asthma (e.g., active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g., allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).
2. Any disorder, including but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:
 - Affect the safety of the subject throughout the study
 - Influence the findings of the studies or their interpretations
 - Impede the subject's ability to complete the entire duration of study
3. Known history of allergy or reaction to any component of the IP formulation.
4. History of anaphylaxis following any biologic therapy
5. A helminth parasitic infection diagnosed within 6 months prior to enrolment (Visit 1) that has not been treated with, or has failed to respond to, standard of care therapy.
6. History of clinically significant infection, including acute upper or lower respiratory infections, requiring antibiotics or antiviral medication within 30 days prior to enrolment (Visit 1) or during the run-in period.

7. Tuberculosis requiring treatment within the 12 months prior to enrolment (Visit 1).
8. Any clinically significant abnormal findings in physical examination, vital signs, dECG, haematology, clinical chemistry, or urinalysis during the run-in period, which in the opinion of the Investigator, may put the subject at risk because of his/her participation in the study, or may influence the results of the study, or the subject's ability to complete entire duration of the study.
9. History of chronic alcohol or drug abuse within 12 months of the enrolment visit, or a condition associated with poor compliance as judged by the Investigator.
10. Positive hepatitis B surface antigen or hepatitis C virus antibody serology. Subjects with a history of hepatitis B vaccination without a history of hepatitis B are allowed to be enrolled.
11. History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at enrolment, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.
12. Current tobacco smoking (smoking must have stopped for ≥ 3 months prior to enrolment) or a history of tobacco smoking for ≥ 10 pack-years (one pack year = 20 cigarettes smoked per day for 1 year).
13. History of cancer:
 - Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to enrolment (Visit 1).
 - Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to enrolment (Visit 1).
14. Use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, systemic corticosteroids including regular treatment with OCS and intramuscular long-acting depot corticosteroids, or any experimental anti-inflammatory therapy) within 3 months prior to enrolment (Visit 1).
15. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of OCS 30 days prior to the date of enrolment (Visit 1) or during the screening/run-in period.
16. [Receipt](#) of immunoglobulin or blood products within 30 days prior to enrolment (Visit 1).

17. Receipt of any marketed or investigational biologic agent (e.g. omalizumab) within 4 months or 5 half-lives prior to the enrolment visit, whichever is longer.
18. Receipt of live attenuated vaccines 30 days prior to the date of randomization and during the study including the follow-up period.
 - Receipt of inactive/killed vaccinations (e.g., inactive influenza) are allowed, provided they are not administered within 5 days before/after any study visit.
19. Receipt of any investigational non-biologic agent within 30 days or 5 half-lives prior to enrolment (Visit 1), whichever is longer.
20. Previous receipt of tralokinumab (CAT-354).
21. Initiation of new allergen immunotherapy or change in existing immunotherapy is not allowed within 30 days prior to enrolment (Visit 1). However, allergen immunotherapy initiated prior to this period may be continued provided there is a span of at least 5 days between the immunotherapy and IP administration.
22. Current use of any oral or ophthalmic non-selective β -adrenergic antagonist (e.g., propranolol).
23. Current use of five-lipoxygenase inhibitors (e.g. Zileuton) or roflumilast.
24. Subjects that have undergone bronchial thermoplasty.
25. Major surgery within 8 weeks prior to the enrolment visit, or planned in-subject surgery or hospitalization during the study period.
26. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 2.5 times the upper limit of normal (ULN) at enrolment.
27. Pregnant, currently breast-feeding, or lactating women.
28. Previous randomization in the present study.
29. Concurrent enrolment in another clinical study where the subject is receiving an IP.
30. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
31. Employees of the clinical study site or any other individuals directly involved with the planning or conduct of the study, or immediate family members of such individuals.

32. Individuals who are legally institutionalized.

For exclusion from the voluntary pharmacogenetic research:

33. Previous allogeneic bone marrow transplant.
34. Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

For procedures for withdrawal of incorrectly enrolled subjects see [Section 3.4](#).

3.3 Subject enrolment and randomization

Investigator(s) should keep a record (i.e., a subject screening log) of subjects who entered pre-study screening. The pre-screening/screening log will be evaluated periodically by AstraZeneca and/or its delegates during routine monitoring visits.

The Investigator(s) will:

1. Obtain signed informed consent or assent from the potential subject, or their guardian/legal representative, before any study specific procedures are performed.
2. Assign the potential subject a unique enrolment number (which begins with an 'E').
3. Determine subject eligibility. See [Section 3](#).
4. Assign the eligible subject unique randomization code via the Interactive Web Response System/ Interactive Voice Response System (IWRS/IVRS).
5. Subjects will be allocated to receive tralokinumab or placebo in a 2:1:2:1 ratio (i.e. 380 subjects on active vs. 190 subjects on placebo, in each of the Q2W and Q4 week regimens). Randomization numbers will be grouped in blocks. Randomized subjects who discontinue will not be replaced. If a subject withdraws from participation in the study, then his/her enrolment/ randomization code cannot be reused.

Specific information concerning the use of the IWRS/IVRS will be provided in a separate instruction manual.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive study medication. There can be no exceptions to this rule. Subjects

who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Randomization codes will be assigned strictly sequentially in each stratum as subjects become eligible for randomization.

The randomization code will be assigned from a randomization list prepared by an internal AstraZeneca computerized system (Grand). The randomization will be stratified by baseline serum periostin (<16.44 ng/mL or ≥ 16.44 ng/mL) sampled during run-in, age and geographical region (i.e. Asia Pacific, North America, South America, Central/Eastern Europe, and Western Europe/Rest of World). Stratified randomization is used to allow for evaluation within sub-groups and/or to allow for heterogeneity in placebo exacerbations rates (regions). Randomization will be done in blocks.

3.6 Methods for ensuring blinding

This is a double-blind study in which tralokinumab and placebo are visually distinct from each other. Neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the subjects will be aware of the treatment received. Since tralokinumab and placebo are visually distinct, IP will be handled by an unblinded IP manager at the site and will be administered by an unblinded investigational site study team member who will not be involved in the management of study subjects. (This could be the same person).

Should an issue arise with the IP (e.g. damaged kit or syringe that has been assigned to a subject prior to administration, or any other unexpected event with the kit or syringe (e.g. a malfunction during IP administration) the unblinded IP manager at the site will contact a predetermined unblinded AstraZeneca site monitor (who is not otherwise involved in the project) to determine whether any specific actions are required.

A blinded AstraZeneca site monitor will perform IP accountability. In the event that the treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, or needs to be known to treat an individual subject for an AE, the sponsor must be notified *immediately* by the investigator and if possible, before unblinding.

All packaging and labelling of IP will be done in such way as to ensure blinding for all sponsor and investigational site staff (other than the unblinded IP manager who will directly handle the pre-filled syringes).

The following personnel will have access to the randomization list:

- those carrying out the packaging and labelling of IP
- those generating the randomization list

The information in the randomization list will be kept from other personnel involved in the conduct of the study, and in a secure location until the end of the study.

No member of the extended study team at AstraZeneca, or any CRO handling data, will have access to the randomization scheme during the conduct of the study, with the exception of the Supply Chain Study Management department and the Patient Safety department at AstraZeneca and personnel at the bioanalytical lab performing the PK sample analysis.

A DSMB will review safety data by assessing the safety of the interventions for adolescents only. The DSMB will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing (see Section 6.8.2), if and as required. The personnel involved in the clinical study at AstraZeneca will remain blinded to these analyses and will have no knowledge of the results presented to the DSMB.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) or pharmacists at the study sites from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

3.8 Restrictions during and after the study

- (a) Fertile and sexually active female subjects (including adolescent females) should use highly effective contraceptive methods throughout the study and at least for 16 weeks (5 half-lives) after last administration of the IP.

- (b) Subjects must abstain from donating blood, plasma from the time of informed consent or assent and for 16 weeks (5 half-lives) after last dose of IP.

3.9 Discontinuation of investigational product

At any time, subjects are free to discontinue IP or withdraw from the study (i.e., IP and assessments – see Section 3.10), without prejudice to further treatment. A subject that decides to discontinue the IP will always be asked about the reason(s) for their decision to withdrawal and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (as described in Section 6); the enrolment/randomization code of the withdrawn subject cannot be reused.

3.9.1 Procedures for discontinuation of a subject from investigational product

Subjects will be discontinued from IP in the following situations:

1. Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
2. The subject experiences an AE that, in the opinion of the Investigator, contraindicates further dosing
3. The development of any risk to the subject as judged by the Investigator or AstraZeneca
4. Severe non-compliance with the study protocol
5. Pregnancy
6. Lost to follow-up¹
7. Development of any study specific criteria for discontinuation, including:
 - a) An anaphylactic reaction to the IP requiring administration of epinephrine
 - b) A helminth parasitic infestation requiring hospitalization
 - c) An asthma-related event requiring intubation
 - d) Any malignancy
8. Development of one or more of the following:
 - a) Confirmed ALT or AST increase of ≥ 8 x ULN
 - b) Confirmed ALT or AST increase of ≥ 5 x ULN for more than 2 weeks
 - c) Confirmed ALT or AST increase of ≥ 3 x ULN and total bilirubin of ≥ 2 x ULN
 - d) ALT or AST of ≥ 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($\geq 5\%$)

¹ A subject is considered lost to follow up when any of the following attempts of contact are failed: 3 attempts of either phone calls, faxes or emails; having sent 1 registered letter/certified mail; or one unsuccessful effort to check the status of the subject using publicly available sources, if allowed by local regulations.

Subjects who discontinue IP or the study will always be asked about the reason(s) for discontinuation and the presence of any AEs. The Principal Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (see [Section 6](#)) and any questionnaires (e.g., for patient reported outcomes) are to be completed.

Discontinuation of IP does not necessarily mean discontinuation of follow-up or termination of study participation. Compliant subjects who are discontinued from the IP should be encouraged to continue to undergo all study related visits/procedures for the full 52-week study period in order to support the final efficacy and safety analysis for tralokinumab (see [Section 8](#)). The reason for premature discontinuation of IP will be documented in the source documentation and recorded in the electronic case report form (eCRF).

It is essential to collect as much data as possible for all subjects throughout the study and especially all potential endpoint events. Complete withdrawal from the study (i.e., withdrawal of consent) has a direct negative impact on the potential validity of all study data and should be avoided wherever possible.

If the subject permanently discontinues IP prior to their completion of the study and wishes to continue with the study assessments, they may choose from 3 different follow-up options, as described in [Section 4.2](#).

For subjects who wish to withdraw from the study completely, refer to [Section 3.10](#)

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screen failures are subjects who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These subjects should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (i.e., subject does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures, and not randomized subjects.

3.10.2 Withdrawal of the informed consent or assent

Subjects are free to withdraw from the study at any time (i.e., from receiving IP and/or having assessments performed), without prejudice to further treatment.

A subject who withdraws their consent or assent will always be asked about the reason(s) for their decision to withdraw, and the presence of any AE. The Investigator will follow up AEs outside of the clinical study. The subject must return the ePRO and ePEF devices.

If a subject withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

If the subject only withdraws consent for the retention of blood samples for future exploratory use (e.g., DNA, study of markers of asthma, identifying potential new drug targets for asthma, or for assay development purposes), the subject will not be withdrawn from the study.

Withdrawal of consent from the study must be ascertained and documented by the Investigator and recorded in the eCRF as well as in the Informed Consent Form (ICF) or assent form. The ICF or assent form must be re-signed and dated by both the subject and the investigator.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan

Assessment/ activity	Enrol- -ment	Run -in	Random- ization	Treatment														EOT	FU	FU	IPD	UNS ¹			
	V1 ²	V2 ³	V3	V4	V5	V6	V7	V8	V9, V10	V11	V12, V13, V14	V15	V16	V17, V18	V19	V20, V21, V22	V23	V24, V25, V26	V27, V28	V29	V30	V31			
	w-6 to -4	w-2	w0	w2	w4	w6	w8	w10	w12 w14	w16	w18 w20 w22	w24	w26	w28 w30	w32	w34 w36 w38	w40	w42 w44 w46	w48 w50	w52	w56	w72			
	42 (-3) days	Visit window (days) ⁴																							
		-3	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	N/A	N/A

¹ At unscheduled visits for assessing an asthma exacerbation, at a minimum, these assessments need to be performed. Other unscheduled visits may be initiated as needed, and the assessments performed as per investigator's judgement.

² Visit 1 can be performed over a period of 3-working days, with the exception of documentation of informed consent and assent (if applicable), which can be completed up to 30 days prior to Visit 1.

³ The run-in period can be 28 to 45 days in duration. Visit 1 should be completed within days -45 to -28. V2 should occur within days -17 to -14, which includes a 3 day window. V3 is considered day 0.

⁴ All visits are to be scheduled from the date of randomization but not from the date of previous visit

Assessment/ activity	Enrol- ment	Run -in	Random- ization	Treatment																EOT	FU	FU	IPD	UNS			
				V4	V5	V6	V7	V8	V9, V10	V11	V12, V13, V14	V15	V16	V17, V18	V19	V20, V21, V22	V23	V24, V25, V26	V27, V28								
				w2	w4	w6	w8	w10	w12 w14	w16	w18 w20 w22	w24	w26	w28 w30	w32	w34 w36 w38	w40	w42 w44 w46	w48 w50								
42 (±3) days				Visit window (days) ⁴																							
	V1 ²	V2 ³	V3	V4	V5	V6	V7	V8	V9, V10	V11	V12, V13, V14	V15	V16	V17, V18	V19	V20, V21, V22	V23	V24, V25, V26	V27, V28	V29	V30	V31					
	w-6 to -4	w-2	w0	w2	w4	w6	w8	w10	w12 w14	w16	w18 w20 w22	w24	w26	w28 w30	w32	w34 w36 w38	w40	w42 w44 w46	w48 w50	w52	w56	w72					
Informed consent/ assent	X																										
	X																										
Informed consent/ assent for DNA analysis (if applicable)	X																										
	X																										
Inclusion/ Exclusion Criteria	X	X	X																								
	X																										
Demographi cs	X																										
	X																										
Medical and asthma history	X																										
	X																										
Complete Physical examination	X		X																	X					X		
	X																										
Brief Physical examination					X		X		X (V9 only y)	X	X (V13 only)	X			X (V1 7 only y)	X	X (V21 only)	X	X (V27 (V27 only)		X					X	

Assessment/ activity	Enrol- ment	Run -in	Random- ization	Treatment																EOT	FU	FU	IPD	UNS ¹
				V4	V5	V6	V7	V8	V9, V10	V11	V12, V13, V14	V15	V16	V17, V18	V19	V20, V21, V22	V23	V24, V25, V26	V27, V28					
	w-6 to -4	w-2	w0	w2	w4	w6	w8	w10	w12 w14	w16	w18 w20 w22	w24	w26	w28 w30	w32	w34 w36 w38	w40	w42 w44 w46	w48 w50	w56	w72			
	42 (±3) days		Visit window (days) ⁴																					
		-3	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	N/A	N/A	
Height	X																			X ⁵				
Weight	X		X									X								X			X	
Vital Signs	X	X	X ⁶	X ⁵	X ⁵	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
dECG	X																			X				
Clinical Chemistry	X		X		X		X					X					X			X		X	X	
Haematolog y	X		X	X	X	X	X	X (we ek 12 only y)	X	X (wee k 20 only)	X		X (we ek 28 only y)	X	X (wee k 36 only)	X	X (44 only)	X (wee k 48 only)	X	X		X	X	
Urinalysis (dipstick) ⁷	X		X		X		X						X							X		X	X	
Urine pregnancy			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	

⁵ Height assessed for adolescent subjects only.
⁶ Vital signs will be taken pre-dose prior to administration of IP. Subjects will be observed 2 hours post treatment for visits 3, 4, 5 and 6. For all other visits where IP is administered, subjects will be observed for a minimum of 1 hour.
⁷ Urine Sample will only be sent to central lab for urinalysis if any dipstick parameters are assessed as abnormal.

Assessment/ activity	Enrol- ment	Run -in	Random- ization	Treatment																		EOT	FU	FU	IPD	UNS ¹					
				V4	V5	V6	V7	V8	V9, V10	V11	V12, V13, V14	V15	V16	V17, V18	V19	V20, V21, V22	V23	V24, V25, V26	V27, V28												
				w2	w4	w6	w8	w10	w12 w14	w16	w18 w20 w22	w24	w26	w28 w30	w32	w34 w36 w38	w40	w42 w44 w46	w48 w50												
	V1 ²	V2 ³	V3																												
	w-6 to -4	w-2	w0																												
	42 (±3) days			Visit window (days) ⁴																											
		-3	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	N/A	N/A						
test (dipstick) ⁸																															
Total IgE			X																		X										
Phadiatop			X																												
Serology (Hepatitis B, C; HIV- 1; HIV-2)	X																														
Serum β- HCG	X																														
FSH ⁹	X																														
Run-in Reversibility		X ₁₀	X ¹⁰																												
ACQ-6 at the site ¹¹	X		X																		X										X

⁸ For WOCBP and adolescent females, urine pregnancy test (dipstick) will only be performed at treatment visits, prior to IP administration.

⁹ FSH test done only for female subjects to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month

¹⁰ For reversibility assessment at Visit 2 (and Visit 3, if required) the full procedure as defined in section 5.1.2.1 should be followed until the subject either meets the FEV1 reversibility requirement (≥12% and ≥200 mL) or completes all steps.

¹¹ ACQ-6 performed at the site unless completed at home the day prior.

Assessment/ activity	Enrol- ment	Run -in	Random- ization	Treatment																EOT	FU	FU	IPD	UNS ¹
				V4	V5	V6	V7	V8	V9, V10	V11	V12, V13, V14	V15	V16	V17, V18	V19	V20, V21, V22	V23	V24, V25, V26	V27, V28					
	w-6 to -4	w-2	w4	w6	w8	w10	w12 w14	w16	w18 w20 w22	w24	w26	w28 w30	w32	w34 w36 w38	w40	w42 w44 w46	w48 w50	w52 w56 w72						
	42 (±3) days		Visit window (days) ⁴																					
		-3	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	N/A	N/A	
ACQ-6 adherence check			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		
AQLQ (S) +12, WPAI+CIQ, EQ-5D-5L at the site ¹²			X																			X		
AQLQ (S) +12, WPAI+CIQ, EQ-5D-5L adherence check			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		
Health care resource utilization	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		
CGIC						X		X (V9 only)	X		X											X		
Asthma Daily Diary including		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		

¹² AQLQ (S) +12 performed at the site unless completed at home the day prior.

Assessment/ activity	Enrol- ment	Run -in	Random- ization	Treatment														EOT	FU	FU	IPD	UNS ¹		
	V1 ²	V2 ³	V3	V4	V5	V6	V7	V8	V9, V10	V11	V12, V13, V14	V15	V16	V17, V18	V19	V20, V21, V22	V23	V24, V25, V26	V27, V28	V29	V30	V31		
	w-6 to -4	w-2	w0	w2	w4	w6	w8	w10	w12 w14	w16	w18 w20 w22	w24	w26	w28 w30	w32	w34 w36 w38	w40	w42 w44 w46	w48 w50	w52	w56	w72		
	42 (±3) days			Visit window (days) ⁴																				
		-3	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	N/A	N/A
home peak expiratory flow assessment adherence																								
Spirometry, ePRO and ePEF device training	X																							
Pre-BD, Spirometry	X	X	X	X	X	X	X		X ¹³	X			X		X		X			X		X	X	X
Post-BD, Spirometry		X	X				X ₁₄													X ¹⁴			X ¹⁴	X
PK			X		X		X						X							X		X		
ADA/nAb			X										X								X			
FE _{NO}	X		X		X		X						X										X	
Assessment of asthma exacerbation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X

¹³ Pre-BD Spirometry only at Visit 9 and not at Visit 10

¹⁴ Only step 1 of the reversibility assessment (section 5.1.2.1) is required.

Assessment/ activity	Enrol- ment	Run -in	Random- ization	Treatment																EOT	FU	FU	IPD	UNS ¹
				V4	V5	V6	V7	V8	V9, V10	V11	V12, V13, V14	V15	V16	V17, V18	V19	V20, V21, V22	V23	V24, V25, V26	V27, V28					
				w2	w4	w6	w8	w10	w12 w14	w16	w18 w20 w22	w24	w26	w28 w30	w32	w34 w36 w38	w40	w42 w44 w46	w48 w50					
				42 (±3) days				Visit window (days) ⁴																
		-3	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	N/A	N/A		
S																								
Randomizati on			X																					
Administrati on of IP (Q2W dosing)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Administrati on of IP (Q4W dosing)			X	X	X	X	X	X (we ek 12 onl y)	X (wee k 20 only)	X	X (we ek2 8 onl y)	X	X (wee k 36 only)	X	X (wee k 44 only)	X (wee k 48 only)								
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood sample for perioistin		X	X					X (we ek 12 onl y)				X							X			X		

Assessment/ activity	Enrol- ment	Run -in	Random- ization	Treatment																EOT	FU	FU	IPD	UNS	
	V1 ²	V2 ³	V3	V4	V5	V6	V7	V8	V9, V10	V11	V12, V13, V14	V15	V16	V17, V18	V19	V20, V21, V22	V23	V24, V25, V26	V27, V28	V29	V30	V31			
	w-6 to -4	w-2	w0	w2	w4	w6	w8	w10	w12 w14	w16	w18 w20 w22	w24	w26	w28 w30	w32	w34 w36 w38	w40	w42 w44 w46	w48 w50	w52	w56	w72			
42 (±3) days				Visit window (days) ⁴																					
		-3	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	N/A	N/A
Blood sample DPP4 and other biomarkers		X	X						X (week 12 only)				X								X			X	
Blood sample for DNA (optional)	X ¹⁵																								

ADA = anti-drug antibodies; AE=Adverse event; ACQ-6=Asthma Control Questionnaire 6; ADA=Anti-drug antibodies; AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 Years and Older; β-HCG=Beta Human Chorionic Gonadotropin; BD=Bronchodilator; DNA=Deoxyribonucleic acid; DPP4=Dipeptidyl Peptidase-4; dECG=digital electrocardiogram; EOT =End of Treatment; ePRO=electronic Patient Reported Outcome device; FE_{NO}=Fractional Exhaled Nitric Oxide; FSH= Follicle-stimulating hormone; HIV=Human immunodeficiency virus; IgE=Immunoglobulin E; IPD=Investigational Product Discontinuation Visit; nAb=Neutralizing antibodies; PK=Pharmacokinetic; PRO=Patient Reported Outcome; UNS=Unscheduled Visit

¹⁵ Blood sample for DNA will ideally be obtained from the subject at Visit 1, but may be taken at any later visit if Visit 1 is not suitable.

4.1 Enrolment/run-in period

4.1.1 Enrolment (Visit 1)

Each potential subject who is at, or over the age of majority (as per local law) will provide informed consent prior to any study specific procedures being and undergo assessments applicable for the visit (see [Table 1](#)).

For subjects less than the age of majority, in addition to the subject providing informed assent, the subject's legal guardian must also provide their informed consent.

Subjects may sign the ICF, or assent form, prior to the performance of Visit 1 procedures. With the exception of documentation of informed consent and assent (if applicable), which can be completed up to 30 days prior to Visit 1, all other Visit 1 procedures should be completed within a 1 to 3-working day window. The 3-day window is to enable subjects to return if necessary for the spirometry assessments on a morning when they have had their BD medications withheld in accordance with the spirometry instructions (see [section 5.1.2](#)). The registration of the subject's enrollment via IWRS/IVRS should occur on the day when the Visit 1 procedures are performed.

Visit 1 assessments are primarily concerned with assessing the subject's eligibility (inclusion/exclusion) criteria, including their asthma disease state, the requisite level of severity based on maintenance medications, exacerbation history, and the current level of control based on an initial ACQ-6 score.

Spirometry will also be performed at Visit 1. Subjects must have a pre-BD FEV₁ value <80% of their PNV (<90% for subjects 12 to 17 years of age) in order to proceed in the study as per (Section [3.1](#), criterion [8](#)). If not, the subject will be screen failed.

Other study assessments and procedures to be performed at this visit include the recording of the subject's demographics, a complete physical examination (including height and weight), vital signs, a dECG, recording the subject's medical/surgical history and concomitant medications, collection of blood samples for haematology/clinical chemistry, serology and biomarkers, collection of a urine sample for dipstick and urinalysis (where applicable), and a pregnancy test for WOCBP.

A record of physician-diagnosed asthma, ICS-LABA use, use of other asthma controllers (Section [3.1](#), criteria [4](#), [6](#) and [7](#)), and asthma exacerbations over the prior year (Section [3.1](#), criterion [10](#)) is required source documentation. A subject's verbal history suggestive of asthma symptoms and/or prior asthma exacerbations, but without supporting documentation, is not sufficient to satisfy these inclusion criteria.

4.1.2 Run-in (Visit 2)

The run-in period (i.e., from Visit 1 to Visit 3) should be 4 to 6 weeks (- 3 days) in duration. The subject should remain on their current asthma treatment with no changes throughout the entire run-in period. Assessments applicable for the run-in period are listed in [Table 1](#).

Visit 2 is primarily concerned with evaluating whether lung function meets the respective study eligibility criteria, to collect AE and concomitant medication information, as well as a blood sample for periostin (to be used for stratification at randomization).

The protocol specified reversibility criterion (i.e. inclusion criterion 9) will be assessed at this visit. Should this criterion not be met at Visit 2, subjects must fulfill it at Visit 3 in order to be randomized.

The subject will be supplied with an electronic hand-held spirometer (peak flow meter) to measure the subject's PEF at home, and an ePRO device to record asthma symptoms and complete relevant questionnaires throughout the study (see section 5.2.2 for further details).

Visit 2 may be performed as a telephone visit (for collection of SAE information only) if the subject is confirmed as ineligible for the study (e.g., based on laboratory results from Visit 1, or medical history).

The subject's eligibility should be evaluated at each visit during the run-in period with the relevant documentation entered in the source and eCRF.

4.1.3 Randomization (Visit 3)

Lung function with measurement of morning pre-dose, pre-BD and post-BD FEV₁ will be performed on Visit 3 prior to randomization. Subjects should have a morning pre-BD FEV₁ of $\geq 40\%$ and $< 80\%$ ($< 90\%$ for subjects 12 to 17 years of age) of the subject's PNV, and fulfil the protocol-specified reversibility criterion ($\geq 12\%$ FEV₁ and ≥ 200 mL), if either is not met at visit 2. Other inclusion criteria at randomization will be confirmed at Visit 3.

Before randomization the subject's compliance with their usual asthma controller (ICS-LABA), and any other asthma controller medication, and ePRO completion must be confirmed (see section 3.1, inclusion criteria 18 and 19). The subject should bring the ePRO device to this visit where they will complete the ACQ-6, AQLQ(S)+12, EQ-5D-5L, and the WPAI + CIQ.

If the periostin value measured at Visit 2 is missing at randomization (Visit 3), the subject should not be randomized, nor should any Visit 3 assessments be performed. A new blood sample for periostin should be taken at this visit and a new Visit 3 visit should be re-scheduled to occur 2 weeks later, along with all other Visit 3 assessments.

4.1.4 Re-screening

Subjects who experience an asthma exacerbation within 30 days prior to ICF date or during the screening/run-in phase should be screen failed. They may be re-screened no sooner than 30 days after their last dose of systemic steroids.

Subjects with respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the screening/run-in period may also be re-screened.

Re-screening for the above mentioned reasons is allowed only once for the subject. Subjects should be re-screened no later than 3 months failing initial enrolment.

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits), subjects may potentially be re-screened. These cases should be discussed with the AstraZeneca Study Physician and documented approval for re-screening should be filed in the Investigator Study File (ISF).

IMPORTANT! Re-screening for subjects who have screen-failed due to an ACQ-6 score <1.5 is not allowed.

Any re-screened subject will be re-enrolled and reassigned their originally assigned enrolment number after signing a new Informed Consent Form (ICF), or assent form, and after all run-in assessments have been performed as listed in [Table 1](#) (with the exception of testing for HIV1 and HIV2, hepatitis B and C, and FSH).

Re-enrolment is only allowed once for any subject, regardless of whether this is due to an exacerbation or infection. The subject may not be re-screened if any other eligibility criteria are failed.

4.2 Treatment period

Inclusion criteria at randomization will be confirmed at Visit 3. Before randomization the subject's compliance with their usual asthma controller ICS-LABA and other asthma controller medication, and ePRO completion must be confirmed (see section [3.1](#), inclusion criteria [18](#) and [19](#)).

Subjects confirmed as eligible will be randomized at Visit 3 (Week 0) in a 2:1:2:1 ratio (i.e. 380 subjects on active, and 190 subjects on placebo, in both the Q2W and Q4W dosing regimen groups) to receive either:

- Tralokinumab 300 mg, or placebo, Q2W (26 doses) or,
- Tralokinumab 300 mg, or placebo, Q4W (13 doses)

The first dose of the IP will be administered following randomization through IWRS/IVRS at Visit 3.

Following randomization the subject will receive 52 weeks of double-blind treatment, with the last dose of tralokinumab/placebo administered at Visit 28 (Week 50) for the Q2W dosing regimen, and Visit 27 (Week 48) for the Q4W dosing regimen.

Subjects will have scheduled visits at 2-week intervals to complete protocol-specific assessments and IP administration, as listed in [Table 1](#). Restrictions as set out in section [7.7.2](#) will continue to apply throughout the treatment period. In case of an asthma worsening/exacerbation (see section [5.1.1](#)), subjects should be evaluated at the study site, when feasible, at an unscheduled visit, or ordinary visit if the worsening happens to fall within a scheduled visit window.

Subjects will continue to measure their PEF at home, as well as record asthma symptoms and responses to questionnaires in the Asthma Daily Diary throughout the 52-week treatment period (see section [5.2.2](#) for details).

Subjects will have brief physical exams performed at times listed in [Table 1](#). A complete physical exam will be performed at Visit 29 (Week 52).

Additional blood samples will be obtained from the subjects at Visits 3, 9, 16 and 29 to further explore the relationship between the clinical response to 2 dosing regimens of tralokinumab and biomarkers.

The subject's adherence for completing all questionnaires in the ePRO will be assessed at all visits during the treatment period, with retraining provided as required.

At Week 52 subjects will come to the site for the End of Treatment (EOT) visit. The subject should bring the ePRO device to the EOT visit and complete the ACQ-6, AQLQ(S)+12, EQ-5D-5L, and the WPAI + CIQ, unless they have been completed at home prior to the visit.

Subjects who prematurely discontinue IP (see section [3.9](#)) should return to the study site and complete procedures described for the IP Discontinuation Visit (IPD visit), see [Table 1](#). At the IP Discontinuation visit, the subject will be given three options as to how they will be followed up as follows:

1. Ideally, the subject should be encouraged to return for all regular clinic visits and perform all scheduled assessments until he/she completes a total of 52 weeks in the study, or,
2. The subject will be offered to be followed up on a monthly basis via telephone calls while continuing eDiary completion, until the subject completes 52 weeks in the study. No further procedures will be performed. Or,
3. If the subject cannot comply or does not wish to comply with the options above, the Investigator will only contact the subject at 52 weeks post randomization. No other study assessments will be performed prior to this contact.

After this period, the subjects will perform the EOT visit as described above.

The key elements to be collected at these follow up visits or telephone contacts for options 2 and 3 are AEs/SAEs, changes in concomitant medications, and asthma exacerbation information. For option 1, all procedures will be done at each visit as indicated in [Table 1](#).

The subject's decision needs to be documented in the eCRF and the specific section in the ICF/assent form addendum needs to be signed by the subject.

Should the subject choose option 3 above, they will complete the IP Discontinuation visit immediately and then a follow up telephone call at week 52. If the subject chooses either option 1 or 2, they will complete the IP Discontinuation visit immediately and then the EOT visit at week 52. The EOT visit will be completed immediately in the case of subsequent early withdrawal from option 1 or 2.

Subjects who initially chose options 1 or 2 and subsequently cannot or do not wish to comply with the requirements of the chosen option, can choose to continue with a less invasive option (i.e.: Subject initially choosing option 1 can continue with 2 or 3, subjects initially choosing option 2 can continue with 3).

The final follow up visits (i.e., 30 and 31) are to occur 4 weeks (+7 days) and 20 weeks (+7 days) from the date of the EOT visit, respectively.

Subjects who do not wish to have any follow up contacts at all, will be discontinued from the study. All discontinued subjects must return the ePRO and ePEF devices at the EOT visit.

Completion, or early termination of IP treatment, will be registered via the IWRS/IVRS for each subject.

4.3 Follow-up period

Subjects will have follow-up visits (30 and 31) at Weeks 56 and 72, respectively.

5. STUDY ASSESSMENTS

The Rave[®] Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site upon completion of the study.

5.1 Efficacy assessments

5.1.1 Assessment of asthma exacerbations

For the purpose of the protocol, an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- Use of systemic corticosteroids for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids
- An ER or urgent care visit (defined as evaluation and treatment for <24 hours in an ER or urgent care center) due to asthma that required systemic corticosteroids (as per above)
- An inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma.

The ePRO device will be programmed to alert both the subject and study site when certain pre-specified worsening thresholds are crossed as follows:

- Decrease in morning peak flow $\geq 30\%$ on at least 2 of 3 successive days compared with baseline (last 10 days of run-in), and/or
- A $\geq 50\%$ increase in rescue medication or one new or additional nebulized β_2 -agonist on at least 2 of 3 successive days compared with the average use for the previous week, and/or
- Nocturnal awakening due to asthma requiring rescue medication use for at least 2 of 3 successive nights, and/or;
- An increase in total asthma symptom score (the sum of day time [evening assessment] and night-time [morning assessment] of at least 2 units above the run-in average (last 10 days of run-in), or the highest possible score (daily score of 6), on at least 2 of 3 successive days.

For the purpose of the protocol, worsening of asthma is defined as new or increased symptoms and/or signs (i.e., physical examination or lung function) that can be either concerning to the subject (subject-driven) or related to an Asthma Daily Diary alert (diary-driven).

If an exacerbation event is not associated with deterioration in at least one of the pre-specified subject –driven and/or diary-driven objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

In order to calculate the number of exacerbations experienced by a subject during the 52-week treatment period, the following rule will be applied:

- The start of an exacerbation is defined as the start date of systemic corticosteroids, ER or urgent care visit requiring systemic corticosteroids, or hospital admission due

to asthma, whichever occurs earlier, and the end date is defined as the last day of systemic corticosteroids, ER or urgent care visit, or hospital discharge, whichever occurs later.

Additional systemic corticosteroid treatments, ER or urgent care visits requiring use of systemic corticosteroids, or inpatient hospitalization due to asthma occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled.

The subject may remain in the study after an exacerbation and continue to receive IP if the Investigator judges that it is medically appropriate for the subject to do so.

Reasonable attempts should be made by the Investigator to bring the subject into the study site for evaluation of a diary alert or subject initiated asthma worsening, particularly when it results in additional treatment being prescribed. Study site evaluations for asthma worsening may occur as an unscheduled visit or as part of an ordinary site visit if the worsening happens to be coincident with a scheduled visit window.

A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study sites (e.g., by the primary care health care provider or at an ER/hospital) and details entered into the exacerbation eCRF module in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

Maximum follow-up time for a subject is approximately 52 weeks; defined as the time from randomization (Visit 3) to the date of Visit 29. For a subject lost to follow-up, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed (i.e., the last contact date).

Exacerbations that occur after a subject has discontinued IP should still be accounted for when deriving the total number of exacerbations; and likewise, the follow-up time will reflect the follow-up time regardless of whether or not the subject is still on IP.

5.1.2 Spirometry

General requirements

FEV₁ will be measured by spirometry at the study site using equipment provided by central vendor. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines ([Miller et al 2005](#)).

The vendor providing central spirometry services will be responsible for assuring that the spirometer used by each site meets ATS/ERS recommendations, and that the study site personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Time of day for scheduled site visit spirometry

For adult subjects, spirometry testing must be initiated in the morning between 6:00 AM and 11 AM according to the schedule provided in [Table 1](#). For adolescent subjects, spirometry testing can be initiated during the whole day according to the schedule provided in [Table 1](#). All post-randomization spirometry assessments should be performed within ± 1.5 hours of the time that the randomization spirometry was performed. For example, if the randomization spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Important! Subjects should be instructed not to use their maintenance twice daily LABA (or ICS-LABA) within 12 hours of the scheduled site visit spirometry as this will affect the pre-BD FEV₁ value; they may be taken subsequently, at the site. For once daily BDs and theophylline a 48 hour washout period is required. **For the same reason subjects should not use their SABA within 6 hours of scheduled spirometry/dECG assessments.** This restriction is particularly critical for efficacy measures taken during the treatment period, but should also facilitate meeting the run-in FEV₁ and reversibility eligibility criteria.

Options for handling subjects who have inadvertently taken their asthma medication within the restricted window are described in section [7.7.2](#).

Spirometry technique

Subjects should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Subjects should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the site. All spirometry manoeuvres (irrespective of whether to obtain values for FEV₁, FVC, FEF 25-75%) should be performed with the subject seated in an upright position. If this is not comfortable for the subject, standing is permitted. The same position should be used by the subject for each forced expiratory manoeuvre from enrolment throughout the study. The head must not be tilted during manoeuvres and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the manoeuvre. Mouthpieces of the same dimension and shape should be used by the subject from enrolment throughout the study.

The spirometry manoeuvre consists of three phases; the first is maximal inspiration, the second is a “blast” of exhalation (to obtain the FEV₁ value) and the last is a continuation to complete exhalation. The subject should inhale rapidly and completely from functional residual capacity. It is important that the preceding inspiration is fast and that any pause at full inspiration be minimal (i.e. only for 1-2s). The subject should be prompted to “blast”, not just “blow”, and they should be encouraged to fully exhale until the end of test criteria are met. If the patient feels dizzy, the manoeuvre should be stopped, since syncope could follow due to prolonged interruption of venous return to the thorax. Manoeuvres that do not meet the end of test criteria should not be used to satisfy the requirement of three acceptable manoeuvres. However early termination, by itself, is not a reason to eliminate all the results from such a manoeuvre from further consideration.

To allow recording of the FVC value, it is important that the whole manoeuvre lasts for at least 6 seconds. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak or obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each spirometry session. There should be at least 3 efforts that meet ATS/ERS acceptability criteria with the highest value and second highest value for FEV₁ and FVC meeting the ATS/ERS reproducibility criteria. The largest FVC and the largest FEV₁ should be recorded after examining the data from all of the usable curves, even if they do not come from the same curve. If the criteria for acceptability and reproducibility are not met with the first 3 expiratory efforts, then additional attempts are required up to a maximum of 8. If the reproducibility criteria is not fulfilled after the maximum number of manoeuvres has been performed, the highest of the FEV₁ and FVC value that is deemed acceptable should be selected. The absolute measurement (for FEV₁), and the percentage of PNV ([Quanjer et al 2012](#)) will be recorded.

The mean forced expiratory flow between 25% and 75% of the FVC (FEF25–75%) is taken from the blow with the largest sum of FEV₁ and FVC. The FEF25–75% must be measured with an accuracy of at least +5% of reading or +0.2 L whichever is greater. It is highly dependent on the validity of the FVC measurement and the level of expiratory effort.

Order of administration of usual asthma controller medication and IP relative to scheduled pre-and post-BD spirometry.

On visits when spirometry is performed the subject's usual asthma controller medication should be withheld until the whole procedure for spirometry has been completed; usual asthma controller may be given after final post-BD spirometry. IP dosing should also be withheld until pre-BD spirometry has been completed.

Record keeping

A signed and dated copy of the pre- and post- BD printout must be kept at the study site for source data verification. The printout must be marked with the study code, subject enrolment code, date and time of measurement, and visit number.

Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the subjects PNV values and are pre-programmed into the spirometer ([Quanjer et al 2012](#)).

FEV₁, expressed as percent of the PNV, will be calculated as follows:

$$\text{FEV}_1\% \text{ of PNV} = (\text{FEV}_1 \text{ measured} / \text{FEV}_1 \text{ PNV}) \times 100$$

5.1.2.1 Reversibility test and post-BD FEV₁ efficacy assessment

Complete the initial (pre-BD) FEV₁ measurement (Section 5.1.2) before commencing the post-BD assessment.

As before, it is important that the subject has withheld each of their theophylline and BD medications for the minimum period of time specified in Section 7.7.2 and Appendix H. If at Visit 2 or Visit 3 the subject has not adhered to this restriction the reversibility assessment should be re-scheduled within the next 7 days; other assessments for the visit can be completed as planned.

Albuterol 90µg metered dose or Salbutamol 100µg metered dose will be used in the reversibility assessment. Up to 8 doses may be administered at Visit 2 and 3, and up to 4 doses at the other visits (Visit 7, Visit 29 (EOT) and/or IP Discontinuation Visit). If there is any concern about the effect on the subject's heart rate, tremor or any other safety parameter during the assessment fewer doses can be administered; the reason should be noted in the subject's medical records.

A spacer device should be used for administration of the SABA; nebulizers should not be used. The same bronchodilator and type of device should be used at each visit where reversibility is assessed.

Step 1: FEV₁ measurement after 4 SABA inhalations

For administration of albuterol/salbutamol, the subject will:

- (i) Perform a gentle, complete expiration
- (ii) Inhale Dose 1 of the SABA to TLC and hold their breath for 5-10 seconds before the subject exhales.
- (iii) Rest for approximately 30 seconds before the next dose
- (iv) Repeat this for Dose 2, Dose 3 and Dose 4, resting for a further 15 – 20 minutes after Dose 4

After resting for 15 – 20 minutes FEV₁ is measured following the technique described in Section 5.1.2

Visit 2 and Visit 3: if the inclusion criterion for reversibility is met ($\geq 12\%$ and ≥ 200 mL) this is the end of the reversibility assessment. If it is not met the subject proceeds to Step 2.

Visit 7, Visit 29/EOT and/or IP Discontinuation Visit: this is the end of the reversibility assessment.

Step 2: FEV₁ measurement following a further 2 (total of 6) SABA inhalations (Only at Visit 2 and Visit 3, if assessed)

The subject will repeat the SABA inhalation procedures for Dose 5 and Dose 6. (See Step 1 above for instructions.)

After resting for the 15 – 20 minutes FEV1 will be measured following the technique described in Section 5.1.2

This is the end of the reversibility assessment if either of the following occurs:

- the inclusion criterion for reversibility is met ($\geq 12\%$ and ≥ 200 mL) or
- the incremental change in FEV1 between Step 1 and 2 is $\leq 5\%$ and the inclusion criterion is not met

Subjects proceed to Step 3 if the incremental change in FEV1 between Step 1 and Step 2 is $> 5\%$ and if the criterion for reversibility has not yet been met.

Step 3: FEV1 measurement following a further 2 (total of 8) SABA inhalations (Only at Visit 2, and Visit 3 if assessed)

The subject will repeat the inhalation procedures for Dose 7 and Dose 8, resting for 15 – 20 minutes after Dose 8. (See Step 1 above for instructions.)

After resting for the 15 – 20 minutes FEV1 will be measured following the technique described in Section 5.1.2. The reversibility assessment is now complete.

For subjects who need to perform step 2 and/or step 3 of the reversibility testing at visit 3, the base-line value for the post-BD outcome variable in FEV1 will be derived from the value obtained after step 1.

5.1.3 Home PEF testing

An electronic, hand-held spirometer (peak flow meter) will be provided to the subject at Visit 2, after all respiratory inclusion criteria have been confirmed (see section 3.1).

Home PEF testing will be performed by the subject in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Recording of home PEF should start from the evening of Visit 2 (Week -2) until the morning of Visit 29 (Week 52) using an ePEF meter device. When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

Subjects should perform 3 successive peak flow manoeuvres while sitting or standing, but in the same position at every testing; the highest of the 3 values will be captured for the morning and for the evening manoeuvres.

The investigator/authorized delegate will check subject's adherence to correct use of the peak flow meter at each visit as shown in Table 1 (or on EOT visit if prematurely discontinued from the study).

5.1.4 Periostin

An IUO/PEO assay is being specifically developed and validated as a companion diagnostic for tralokinumab to address the potential identification of a target population with an enhanced response rate based on the presence of high serum periostin as an indicator of IL-13 driven asthma. The performance characteristics of the periostin assay have not been established. No clinical decision or patient notification should be made based on the results obtained with this product.

A baseline periostin concentration level using the investigational assay will be determined for each subject enrolled in the trial. Subject assessment with regards to periostin baseline level at Visit 2, will be used for stratification purposes. Analysis will be performed by the central laboratory. Blood samples will also be obtained at Visits 3, 9, 16, and 29. These samples may be used in existing and/or future clinical studies of in vitro diagnostic assays.

Instructions for sample collection, processing, storage, and shipment will be included in a separate laboratory manual provided to the sites.

5.1.5 Level of fractional exhaled nitric oxide

Method of assessment

Fractional exhaled nitric oxide (FE_{NO}) measurements will be performed at Visits 1, 3, 5, 7, 16, 23, and 29 (see [Table 1](#)). Subjects should not use their rescue SABA medication (e.g., albuterol/salbutamol) within 6 hours of the measurement. Inhaled BDs (including ICS-LABA) should be withheld for the effect duration specific to the BD. If not, the visit must be rescheduled.

Measurements will not be performed until 2 weeks after a respiratory infection. Subjects will be asked whether they have had a respiratory infection in the 2 weeks prior to measurement, which will be recorded as “Yes or No” in the eCRF. Measurement of FE_{NO} will be performed prior to spirometry at every visit.

FE_{NO} will be measured using a chemiluminescence analyzer

. Information concerning the specifications and use of the analyzer will be provided in a separate instruction manual.

The standard single exhalation technique recommended by the ATS will be followed ([Dweik et al 2011](#)).

Signed and dated printouts from the measurements will be kept in the ISF for Source Data Verification (SDV). Printouts will be marked with the study code, subject enrolment/randomization code, date, time of measurement, visit number and subject initials. If a printout cannot be printed, the mean value of the measurements will be recorded in the subject's medical records for SDV.

The vendor supplying the chemiluminescence analyzer to participating sites will be responsible for ensuring that the equipment and procedures for the measurement of FE_{NO} are validated prior to the start of the study.

5.1.6 Safety assessments

5.1.6.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at visits in accordance with the schedule outlined in [Table 1](#). Haematology. Clinical chemistry and urinalysis samples should be collected at unscheduled visits for assessing an asthma exacerbation, at a minimum. Other unscheduled visits may be initiated as needed, and assessments performed as per investigator's judgement. For dosing visits, all samples will be taken prior to the administration of IP.

Detailed schedules of the chemistry, haematology, and urinalysis tests are presented in [Table 2](#), [Table 3](#), [Table 4](#), and [Table 5](#), respectively.

Table 2 List of safety laboratory tests

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum)
B-Haemoglobin	S-Alkaline phosphatase (ALP)
B-Leukocyte count	S-Alanine transaminase (ALT)
B-Leukocyte differential count (absolute count)	S-Aspartate transaminase (AST)
B-Platelet count	S-Bilirubin, total
B-Hematocrit	S-Blood urea nitrogen
B-Mean corpuscular volume	S-Calcium, total
B-Red blood cell (RBC) count	S-Carbon dioxide (CO ₂)
	S-Chloride
	S-Creatinine
	S-Creatinine kinase
Urinalysis	S-CRP
U-Nitrite (dipstick)	S-Gamma-glutamyl transpeptidase (GGT)
U-Bilirubin (dipstick)	S-Glucose
U-Glucose (dipstick)	S-Phosphorus
U-Blood (dipstick)	S-Potassium
U-Protein (dipstick)	S-Sodium
U-Ketones (dipstick)	S-Total cholesterol
Urine microscopy and urine casts (as required)	S-Uric acid
Urine culture (as required)	

Table 3 Clinical chemistry tests schedule

Visit	V1	V3 (Random)	V5	V7	V16	V23	V29	IPD	UNS Visit
Week	-6	0	4	8	26	40	52 (EOT)	N/A	N/A
ALP	X	X	X	X	X	X	X	X	X
ALT	X	X	X	X	X	X	X	X	X
AST	X	X	X	X	X	X	X	X	X
BUN	X	X	X	X	X	X	X	X	X
Calcium, total		X					X	X	X
Chloride		X					X	X	X
CO ₂		X					X	X	X
Creatinine	X	X	X	X	X	X	X	X	X
Creatinine kinase		X							
CRP		X							
GGT	X	X	X	X	X	X	X	X	X
Glucose		X					X	X	X
Phosphorus		X					X	X	X
Potassium		X					X	X	X
Sodium		X					X	X	X
Total bilirubin	X	X	X	X	X	X	X	X	X
Total cholesterol		X					X	X	X
Uric acid		X					X	X	X

Table 4 **Haematology/Haemostasis (whole blood) schedule**

VISIT	V1	V3	V4	V5	V7	V9	V11	V13	V15	V17	V19	V21	V23	V25	V27	V29	V30	V31	IPD	UNS Visit
Week	-6	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52 (EOT)	56 (FU)	72 (FU)	N/A	N/A
B-Haemoglobin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Leukocyte count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Leukocyte differential count (absolute count)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Platelet count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Hematocrit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Mean corpuscular volume	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Red blood cell count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5 **Urinalysis schedule**

VISIT	V1	V3 (Rand)	V 5	V7	V16	V23	V29	IPD	UNS
Week	-6	0	4	8	26	40	52 (EOT)	N/A	N/A
U-Nitrite (dipstick)	X	X	X	X	X	X	X	X	X
U-Bilirubin (dipstick)	X	X	X	X	X	X	X	X	X
U-Glucose (dipstick)	X	X	X	X	X	X	X	X	X
U-Blood (dipstick)	X	X	X	X	X	X	X	X	X
U-Protein (dipstick)	X	X	X	X	X	X	X	X	X
U-Ketones (dipstick)	X	X	X	X	X	X	X	X	X
Urine microscopy and urine casts (as required)*									
Urine culture (as required)*									

* Urine samples will be analyzed locally and sent for analysis at the central lab only when a positive dipstick result for any parameter is observed.

The total volume of blood that will be collected from each subject during the study is presented in [Table 6](#).

* Urine microscopy, casts and culture to be performed only if dipstick result is abnormal

Table 6 **Volume of blood to be drawn from each subject**

Assessment		Sample volume (mL)	No. of samples	Total volume ³ (mL)
Safety	Clinical chemistry	2.5	7	17.5
	Haematology	2	18	36
FSH, β -HCG ¹		1	1	1
Serology		7.5	1	7.5
IgE		2.5	2	5
Phadiatop		2.5	1	2.5
Periostin		6	5	30
DPP4 and other biomarkers		10	5	50
ADA/nAb		3.5	4	14
PK		3.5	6	21
Pharmacogenetics ²		10	1	10
Total				194.5

¹ Female subjects only

² Optional

³ The number of samples may be changed due to additional sampling at unscheduled visits, and the blood volume required may be altered to fit the assay requirements. The total volume of blood drawn from each subject over the course of the study will not exceed 450 mL.

Urine will be tested locally and sent for analysis at the central lab only when a positive dipstick result for any parameter is observed. Blood samples for determination of haematology/haemostasis and clinical chemistry will be performed at a central laboratory. For information on methods of collection, assessment, labeling, storage and shipment of samples please refer to the separate Laboratory Manual.

A copy of the laboratory result report should be signed and dated by the Investigator and retained at the study site.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results report should be signed and dated, and retained at site as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a subject shows an AST **or** ALT $\geq 3 \times \text{ULN}$ **or** total bilirubin $\geq 2 \times \text{ULN}$ please refer to [Appendix E](#), ‘Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy’s Law’, for further instructions.

5.1.6.2 Pregnancy Test

The following tests are applicable to female subjects only, and will be conducted in accordance with the schedule provided in [Table 1](#)

- Serum β -human chorionic gonadotropin (β -HCG) – the test done at enrolment (Visit 1) only, for WOCBP and adolescent females (analyzed at central laboratory)
- FSH – the test done at enrolment (Visit 1) only, for female subjects to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 months
- Urine HCG – the test will be performed at the study site for WOCBP and adolescent females at each treatment visit before IP administration using a dipstick. Positive urine test result must be confirmed with serum β -HCG.

5.1.7 Physical examination

Physical examinations (complete and brief) will be performed in accordance with schedule provided in [Table 1](#).

Baseline data will be collected at Visit 1. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE as described in section [6.1](#).

5.1.7.1 Complete physical examination

The complete physical examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears, nose, mouth, and throat), lymph nodes, abdomen, musculoskeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.

5.1.7.2 Brief physical examination

The brief physical examination will include an assessment of the general appearance, abdomen, cardiovascular and respiratory system. For the brief physical examination only, information on whether the assessment was performed or not will be recorded.

5.1.8 dECG

All ECG assessments must be performed using a digital electrocardiogram (dECG) device. dECGs will be performed in accordance with schedule provided in [Table 1](#). dECG assessments will be performed prior to blood drawing, spirometry, IP administration and BD administration.

For all subjects, the printouts of the dECG will be collected and signed, dated and stored at the study site along with a signed and dated photocopy of each printout (i.e., if the printout is not on archive-quality paper).

5.1.8.1 Resting 12-lead dECG

A 12-lead dECG will be taken in supine position, after the subject has been resting for at least 5 minutes. The assessment should be performed before interventions with the subject (e.g., spirometry and administration of asthma-related medications and IP).

A standard dECG with a recommended paper speed of 50 mm/second covering at least 6 sequential beats will be used. The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential dECG findings. In case of discrepancy between the Investigator's interpretation and that provided by the dECG machine (if applicable), the Investigator's interpretation takes precedence and should be noted on the printout and recorded in the eCRF. Two identical copies of the dECG will be produced and quality checked and kept in case of further need for re-evaluation.

It is highly recommended that the same machine be used for all dECG assessments throughout the subject's participation in the study.

dECG data and evaluation will be performed by the site Investigator and recorded in the eCRF.

5.1.9 Vital signs

Pre-dose vital signs (i.e., pulse, blood pressure, respiration rate and body temperature) will be obtained in accordance with schedule provided in [Table 1](#).

Vital signs will be taken prior to blood drawing, IP administration, and, if possible, usual asthma controller medication. At Visits 3 through 6, subjects should be observed for a minimum of 2 hours after IP administration for the appearance of any acute drug reactions. For the remaining visits involving IP administration, subjects will be observed for a minimum of 1 hour after IP administration for any such reaction.

Vital signs should also be taken prior to per protocol BD administration, if applicable for that visit.

5.1.9.1 Pulse, blood pressure and respiration rate

Pulse rate and blood pressure should be measured after the subject has been resting for at least 5 minutes. The measurement will be taken in sitting position. Pulse rate will be obtained before blood pressure.

Respiration rate will be obtained after subject has been resting for at least 5 minutes, by counting number of breaths (i.e., how many times the chest rises) for one minute.

5.1.9.2 Body temperature

Body temperature will be measured in degrees Celsius prior to IP administration, in accordance with local standards.

5.1.10 Other safety assessments

5.1.10.1 Serology

Hepatitis B surface antigen, hepatitis C antibody, HIV-1 and HIV-2 antibodies will be assessed at enrolment (Visit 1) only. All testing for these will be performed at a central laboratory.

Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

5.1.10.2 Infections

Subjects experiencing a severe infection, defined as/resulting in:

- life-threatening
- requiring hospitalisation
- requiring treatment with antiviral medications, intravenous antibiotics or medications for helminth parasitic infections or,
- a permanent discontinuation of study drug.

All above events must be entered in the infection module in the eCRF.

5.2 Other assessments

5.2.1 Weight and height

Weight and height will be measured in accordance with the schedule provided in [Table 1](#).

Note: height will be measured at enrolment (Visit 1) only.

The subject's weight will be recorded in kilograms, and height will be recorded in centimetres. Weight and height measurements will be performed in light clothing and with shoes off.

5.2.2 Patient reported outcomes

Patient reported outcomes data will be captured using an ePRO. The device will be paired with a handheld spirometer (peak flow meter) for measuring at-home PEF testing (as outlined in section [5.1.3](#)). Subjects will be trained on basic ePRO operation and will subsequently complete the ACQ-6 during Visit 1. After completing the Visit 1 ACQ-6, the device will remain at the site until Visit 2. At Visit 2, the site staff will set assessment reminder alarms on the device and train the subject on at-home use of the ePRO and handheld spirometer. Training will include explanation of device functionality and proper use of the spirometer. The subject will be asked to use both devices as part of the training and will be asked to verify completion of training on the ePRO device. Subjects will be provided with information on device use and issue resolution (e.g., helpdesk numbers) to conclude the training.

At-home PRO assessment will start the evening of Visit 2. Subjects will be asked to bring the device back to the site for Visit 3 for the baseline assessments at the site. Following Visit 3, all PRO data will be collected at home until Visit 29. Additional details concerning the assessments can be found in the subsequent sections (see [sections 5.2.2.1 to 5.2.2.5](#)).

5.2.2.1 Asthma Daily Diary

The Asthma Daily Diary will be completed each day from the evening of Visit 2 to the morning of Visit 29. The Asthma Daily Diary will include the following daily recordings: morning and evening home PEF data (obtained from the home peak flow meter), asthma symptoms, inhalations of rescue medication, nights with awakenings due to asthma symptoms, maintenance medication compliance. There will be triggers in the ePRO device to alert the subjects to signs of worsening of asthma and to contact their physician, please refer to [section 5.1.1](#).

The subject should contact the study physician for evaluation after receiving a diary alert. The investigator/authorized delegate will check subject's adherence to the Asthma Daily Diary at each visit as shown in [Table 1](#).

Home PEF measurement

Details regarding home PEF measurement please refer to [section 5.1.3](#).

Asthma symptoms

Asthma symptoms during night-time and daytime will be recorded by the subject each morning and evening in the Asthma Daily Diary, beginning the evening of Visit 2 until the morning of Visit 29.

Daytime is defined as the time period between the morning lung function assessment (upon rising in the morning) and the evening lung function assessment. Night-time is defined as the time period between the evening lung function assessment (at bedtime) and the morning lung function assessment.

Rescue medication

The number of rescue medication inhalations (puffs) and nebulizer treatments taken will be recorded by the subject in the Asthma Daily Diary twice daily (i.e., in the morning and evening) beginning the evening of Visit 2 until the morning of Visit 29. The number of inhalations taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and the morning will be recorded in the morning.

Nocturnal awakenings

Nocturnal awakenings due to asthma symptoms will be recorded by the subject in the Asthma Daily Diary each morning, beginning in the morning after Visit 2 until the morning of Visit

29, by answering question whether he/she woke up during the night due to asthma symptoms by a “yes” or “no” response.

Maintenance medication

Maintenance medication administration will be recorded in the Asthma Daily Diary once daily in the morning, beginning in the morning after Visit 2 until the morning of Visit 29.

5.2.2.2 Asthma Control Questionnaire (ACQ-6)

The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short-acting β_2 -agonist use) omitting the FEV₁ measurement from the original ACQ score.

Subjects will be asked to recall how their asthma has been during the previous week by responding to 1 question regarding their BD use, and 5 questions pertaining to their asthma symptoms.

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and ≤ 1.5 indicate partly controlled asthma, and a score > 1.5 indicates uncontrolled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful.

The questionnaire will be completed using the ePRO device.

Visit 1 ACQ-6 scores will determine eligibility for run-in and randomization (see section 3.1 inclusion criterion 11). An initial screening ACQ-6 will be taken at Visit 1 at the study site. Subjects will then complete the ACQ-6 at Visit 3, and once randomized, subjects will be asked to complete ACQ-6 once every 2 weeks (± 1 day) throughout the treatment period.

The Investigator/authorized delegate will check subject’s adherence to the ACQ-6 at each visit as shown in Table 1.

5.2.2.3 Standardised Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12)

The AQLQ(S)+12 is a questionnaire that measures the health related quality of health-related quality of life assessment questionnaire developed for asthma subjects ages 12 and above.

The questionnaire comprises 4 separate domains (i.e., asthma symptoms, activity limitations, emotional function, and environmental stimuli).

Subjects will be asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score will be calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function, and

environmental stimuli) are the means of the responses to the questions in each of the domains. Individual improvement in both the overall score and individual domain scores of 0.5 has been identified as a minimally important change. The questionnaire will be completed using the subject's ePRO device.

The AQLQ(S)+12 will be first completed by the subject at the site at Visit 3 (Week 0), then every 4 weeks (± 1 day) throughout the treatment period. At the EOT visit the AQLQ(S)+12 will be completed during the visit unless completed the day prior.

The Investigator/authorized delegate will check the subject's adherence to AQLQ(S)+12 at each visit as shown in [Table 1](#).

5.2.2.4 Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ)

The WPAI+CIQ consists of questions about how asthma and asthma related issues impact a subject's ability to work, attend classes, and perform regular daily activities. The questionnaire relates to the subject's experience over the previous 7 days. The WPAI+CIQ will be used to measure self-reported productivity loss. The questionnaire will be completed using the subject's ePRO device.

The WPAI+CIQ will be first completed at Visit 3 (Week 0), then every 2 weeks (± 1 day) at home throughout 52-week treatment period.

The Investigator/authorized delegate will check subject's adherence to WPAI+CIQ at each visit as shown in [Table 1](#).

5.2.2.5 European quality of life-5 dimensions-5 levels (EQ-5D-5L)

The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty.

The subject will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the subject will be asked to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state

The EQ-5D-5L will be completed weekly (+1 day) starting from Visit 3 (Week 0) throughout Week 52 (Visit 29) using the ePRO device.

The investigator/authorized delegate will check subject's adherence to EQ-5D-5L at each visit as shown in [Table 1](#).

5.2.2.6 Health care resource utilization

Broad-based health care utilization asthma-related event information will be collected by the Investigator/authorized delegate at each visit (as shown in [Table 1](#)) and recorded in the appropriate eCRF module.

At Visit 1, Healthcare Resource Utilization (HRU) information will be collected with a ‘one year’ recall period. All the subsequent visits will collect HRU information with a recall period of ‘since the last scheduled visit’.

Note: cases of hospitalization must also be reported as an SAE (as described in sections [6.2](#) and [6.4](#)).

5.2.2.7 Clinician – Global Impression of Change (CGIC) assessment

The Clinical Global Impression of Change (CGIC) instrument is used to evaluate the overall response to treatment. The investigator (clinician) will be asked to rate the degree to which the overall asthma status may have changed when compared to baseline (i.e. randomization visit/initiation of study drug). The assessment uses a 7-point rating scale: 1 = Very Much Improved; 2 = Much Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; and 7 = Very Much Worse.

The CGIC will be completed at the site visits as indicated in [Table 1](#). It is recommended that the same clinician completes the CGIC at all applicable visits for an individual subject. Before making the assessment the clinician will need to access and review the results from all relevant assessments including lung function measurements (FEV1 and PEF) and patient reported outcomes (Asthma Daily Diary, ACQ-6 and AQLQ) performed before the visit, Adherence to the patient reported outcomes should be closely monitored.

5.3 Pharmacokinetics and Immunogenicity

5.3.1 Collection of samples

Blood samples for determination of tralokinumab in serum will be collected pre-dose at the times presented in [Table 1](#). It is important that date and time of each SC injection and sample collection be recorded for each subject.

Instructions for sample collection, labeling, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

The volume of blood that will be collected from each subject for these assessments is presented in [Table 6](#).

5.3.2 Determination of drug concentration

Samples for determination of tralokinumab concentration in serum will be analyzed by a laboratory on behalf of AstraZeneca, using a validated bioanalytical method. Details of the analytical method used will be described in a bioanalytical report. The PK samples will be

retained for future use at AstraZeneca, or designee, for a maximum of 15 years following the date of Last Subject Last Visit.

A summary of PK analysis results will be reported in the CSR; details of the PK analysis will be reported separately in a bioanalytical report.

5.3.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to the AstraZeneca Biobank; see details in the Laboratory Manual).

5.3.4 Immunogenicity

Instructions for immunogenicity (ADA and nAb) sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

Samples used for immunogenicity analyses will be retained at AstraZeneca or designee for a maximum of 15 years following the Last Subject's Last Visit. A summary of the analysis will be presented in the CSR. Details of the analytical method used will be described in a bioanalytical report.

Anti-tralokinumab antibodies

The pre-dose serum samples to measure presence of ADA will be collected according to the schedule of study procedures (see [Table 1](#)).

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and will be analyzed for the presence of nAb.

Neutralizing antibodies

Neutralizing antibodies will be assessed at Visits 3, 16, 30 and 31 according to the tiered testing scheme outlined above, as well as at any discontinuation, as indicated.

The presence or absence of nAb will be determined using a validated bioanalytical method. A summary of nAb incidence rate will be reported in the CSR and details of the nAb assessment will be reported separately in a bioanalytical report.

5.3.5 Total IgE

Testing for total IgE will be performed at Visits 3 and 29 (Weeks 0 and 52, respectively).

Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

5.3.6 Phadiatop

Testing for phadiatop will be performed at Visit 3 (Week 0). The analysis for these will be performed by central laboratory.

Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

5.4 Pharmacodynamics

5.4.1 Serum biomarkers

Blood (serum) samples will be collected pre-dose according to the schedule in [Table 1](#) to evaluate the pharmacology of tralokinumab, including but not limited to, periostin and DPP4.

The periostin level measured at Visit 2 will also be used for stratification at randomization.

Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites. AstraZeneca or a designee will retain serum biomarker samples for investigation of the pharmacology of tralokinumab for a maximum of 15 years following the last subject's last visit.

The results from the investigation of such samples may not be reported in the CSR but in separate reports and in scientific publications as appropriate.

5.5 Pharmacogenetics

5.5.1 Collection of pharmacogenetic samples (optional)

The collection of blood for a DNA sample for pharmacogenetic research is optional. Should the subject wish to provide a sample for this research, their consent or assent to participate in the pharmacogenetic research components of the study is mandatory. Should a subject not wish to provide a sample for this research, he/she will still be allowed to participate in the main study.

The blood sample for genetic research should be obtained from the subjects at Visit 1 (i.e., at enrolment). Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an AE, such subjects would be important to include in any genetic analysis. If for any reason the sample is

not drawn at Visit 1 it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

5.5.2 Storage, re-use and destruction of pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the Clinical Study Report itself, as an addendum, or separately in a scientific report or publication.

For all samples, irrespective of the type of coding used, DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (i.e., an AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent or assent when the subject has requested disposal/destruction of collected samples not yet analyzed.

5.6 Biomarker analysis

The subject's consent or assent to the use of donated biological samples for non-exploratory analysis purposes is mandatory.

Biological samples (i.e., blood, plasma, serum) will be collected and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

5.6.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with

biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.6.2 Labelling and shipment of biological samples

The Principal Investigator will ensure that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see [Appendix C](#) 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials will not be shipped and no further samples will be taken from the subject unless agreed with AstraZeneca, and appropriate labelling, shipment and containment provisions are approved.

5.6.3 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their lifecycle.

The Principal Investigator, or delegate, at each site will keep full traceability of collected biological samples from the subjects while in storage at the site until shipment or disposal (where appropriate), along with documentation of receipt of arrival.

The sample receiver will keep full traceability of the samples while in storage and during use until used, or disposed of, or until further shipment along with documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use will be registered in _____ or designate during their entire life cycle.

5.6.4 Withdrawal of Informed Consent or Assent for donated biological samples

If a subject withdraws consent or assent to the use of their donated biological samples that will be used for non-exploratory purposes, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research. As collection of the biological samples that will be used for non-exploratory purposes, is an integral part of the study, the subject will be withdrawn from further study participation. Subjects who withdraw their consent/assent for the use of their samples to be used for exploratory/future use purposes, will be allowed to continue in the study.

The Principal Investigator will be responsible for ensuring that:

- The subject's withdrawal of informed consent or assent to the use of donated samples is notified immediately to AstraZeneca

- The biological samples from any subject who withdraws consent or assent to the use of these samples, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- The laboratory(ies) holding the samples is/are informed about the withdrawn consent or assent immediately, and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site
- The subject and AstraZeneca are informed about the sample disposal.

AstraZeneca will ensure that the central laboratory(ies) holding the samples is/are informed about the withdrawn consent or assent immediately, the samples are disposed of/destroyed, and that the action is documented and provided to the study site.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see [Appendix B](#) to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events, including SAEs will be collected from the time the subject signs the informed consent or assent form, throughout the treatment period and the follow-up periods (i.e., Visit 30, Week 56) and Visit 31 (Week 72).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at any follow up visit in the study will be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Adverse event variables

The following variables will be collected in the eCRF for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity* of the AE
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to IP
- AE caused subject's withdrawal from study (yes or no)
- Outcome

*Intensity rating scale:

- 1 mild (awareness of sign or symptom, but easily tolerated)
- 2 moderate (discomfort sufficient to cause interference with normal activities)
- 3 severe (incapacitating, with inability to perform normal activities)

In addition, the following variables (if applicable) will be collected in the eCRF for SAEs:

- Date AE met criteria of serious
- Date Investigator became aware of the SAE
- AE is serious due to
- Date of hospitalization

- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of the AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Assessment of causality

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

A guide to the interpretation of the causality question is provided in [Appendix B](#) to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: ‘*Have you/your child had any health problems since the previous visit/you were last asked*’, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator will use the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT $\geq 3 \times \text{ULN}$ together with total bilirubin $\geq 2 \times \text{ULN}$ may need to be reported as SAEs. Please refer to [Appendix E](#) for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease progression

Symptoms of the disease under study

Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnoea, breathlessness and phlegm, will be recorded as AEs when:

- the sign or symptom is serious according to definitions, see Section [6.2](#),
- the subject discontinues the study due to the sign or symptom, and/or
- the sign or symptom is new to the subject or not consistent with the subject's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the investigator.

Asthma exacerbations should not be recorded as AEs after randomization, unless it fulfils any of the above criteria. All asthma exacerbations should be recorded in the exacerbation eCRF as per section [5.1.1](#).

If a subject discontinues IP due to a study specific discontinuation criterion, this should always be recorded as 'Development of study specific withdrawal' on the termination form in the eCRF. In addition, the investigator must assess whether the asthma deterioration should also be reported as an AE leading to discontinuation of IP (DAE)/AE leading to withdrawal from study on the AE form.

6.4 Reporting of serious adverse events

All SAEs must be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs during the course of the study, Investigators or other site personnel must inform the appropriate AstraZeneca representatives within one day (i.e., immediately) but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Subject Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs, where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel must inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day (i.e., immediately) but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert will be sent to the designated AstraZeneca representative(s).

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative(s) by telephone.

The AstraZeneca representative(s) will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca IP.

6.5 Overdose

An overdose with associated AEs is to be recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF, as well as in the Overdose eCRF module.

An overdose without associated symptoms is only to be reported on the Overdose eCRF module.

If an overdose with the AstraZeneca study drug occurs during the course of the study, the Investigator, or other site personnel, must inform appropriate AstraZeneca representative(s) immediately, and **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Subject Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel will inform the appropriate AstraZeneca representatives within 1 day (i.e., immediately) but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Subject Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy module in the eCRF will be used to report the pregnancy and the pregnancy outcome module will be used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study.

6.7 Management of IP related toxicities

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as well as medical equipment to treat acute anaphylactic reactions must be immediately available when IP is being administered. Study site personnel must be trained to recognize and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in [Appendix G](#).

Anaphylaxis will be defined as serious reaction that is rapid in onset and may cause death (Sampson et al 2006). Anaphylaxis typically manifest as 1 of 3 clinical scenarios:

1. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following: a) respiratory compromise; or b) reduced blood pressure or symptoms of end-organ dysfunction

2. Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms
3. Reduced blood pressure after exposure.

Subjects will have had a pre-assessment (i.e., vital signs and lung function) prior to IP administration. At Visits 3 through 6, subjects should be observed for a minimum of 2 hours after IP administration for the appearance of any acute drug reactions. For the remaining visits involving IP administration, subjects will be observed for a minimum of 1 hour after IP administration for any such reaction.

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn during the event for additional ADA testing (if not already scheduled for this visit). If an anaphylactic reaction occurs, a blood sample will be drawn from the subject as soon as possible after the event, at 60 minutes \pm 30 minutes after the event, and at discharge for analysis of serum tryptase. The sample will be tested at the local lab or central lab where applicable.

6.8 Study governance and oversight

6.8.1 Independent Adjudication Committee

Tralokinumab is being developed for the treatment of severe asthma. There is considerable variation in the severity of subjects who seek ER or urgent care, and in the clinical thresholds used to determine the need for hospitalization.

An independent adjudication committee, blinded to the treatment of the subjects, will evaluate cases of ER or urgent care visits and hospitalizations, as well as all deaths, that occur during the course of the study to confirm that any such event is due to a worsening of asthma. For completeness, the adjudication committee will also be tasked with reviewing cardiovascular, cerebrovascular and malignant adverse events occurring after randomization. The committee will include specialists in pulmonology, cardiology, neurology and oncology and will operate in accordance with dedicated Adjudication Committee Charter/Manual of Operations.

6.8.2 Data and safety monitoring board

An external DSMB will monitor and protect the safety of adolescent subjects throughout the double blind treatment period of the study. The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or subjects.

The DSMB will review safety data on a regular basis as set out in the DSMB charter. The data for review will be outlined in the DSMB charter. The DSMB will have access to individual treatment codes and will be able to merge these with the collected study data while the study

is ongoing. For reference, the DSMB will also have access to study data from adults. Subject enrollment will continue during DSMB review of safety data.

The DSMB will operate in accordance with the dedicated DSMB Charter/Manual of Operations and will be agreed to in advance by the DSMB members.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

All investigational products will be manufactured in accordance with Good Manufacturing Practice (GMP).

Tralokinumab and placebo administered in the study will be a clear to opalescent, colourless to yellow solution free from, or practically free, from visible particles.

Subjects will be randomized at Visit 3 (Week 0) in a 2:1:2:1 ratio to receive either:

- Tralokinumab 300 mg, or placebo, Q2W (26 doses) or,
- Tralokinumab 300 mg, or placebo, Q4W (13 doses)

Each subject will receive two SC injections of 150 mg tralokinumab at each dosing interval to receive a total dose of 300 mg, or placebo. The identity details for the IP are found in [Table 7](#).

Table 7 Identity of investigational product

Investigational product	Concentration and Formulation	Dosage form and strength	Manufacturer
Tralokinumab	Formulated at a nominal concentration of 150 mg/mL in 50mM sodium acetate/acetic acid buffer, 85mM sodium chloride, 0.01% (w/v) PS-80 pH 5.5 solution.	150 mg/mL solution for injection in an accessorized pre-filled syringe, 1.0 mL fill volume.	MedImmune
Placebo	Placebo contains the same excipients, in the same concentration only lacking tralokinumab	Placebo solution for injection in an accessorized pre-filled syringe, 1.0 mL fill volume.	MedImmune

The accessorized pre-filled syringe (APFS) is a single use, disposable system that is designed to administer the labelled dose of the system to the subcutaneous space during one injection

and automatically provide a safety mechanism to reduce the occurrence of accidental needle sticks during disposal of the system.

The APFS consists of a pre-filled syringe sub-assembly (PFS-SA; 1 mL long pre-filled syringe barrel with a 1/2 inch 27 gauge thin wall staked in needle, rigid needle shield, plunger stopper) and a safety device.

7.2 Dose and treatment regimens

The IP will be administered at the study site on treatment visits and within visit windows as specified in [Table 1](#). An interval of minimum 7 days is required between 2 dosing visits.

IP administration

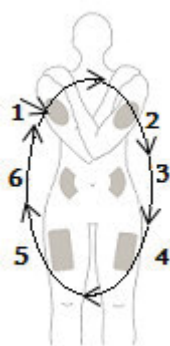
IP will be administered by a qualified, unblinded healthcare professional. The two injections should be administered within the same body location, separated by at least 3 cm. The injection site must be recorded in the source documents at each treatment visit and recorded in the eCRF.

IP **must** be equilibrated to room temperature for a minimum of 30 minutes prior to dose administration.

The person administering the dose will wipe the skin surface of the upper arm, anterior thigh or abdomen with alcohol, and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90-degree angle approximately halfway into the SC tissue. The IP will be slowly injected (at least 5-second duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection.

It is advised that the site of injection of IP be rotated such that the subject receives IP at a different anatomical site at each treatment visit. The suggested injection site rotation sequence is presented below in [Figure 2](#).

Figure 2 Injection sites and rotation scheme



In cases when rotation of the injection site is not favorable for the subject and/or Investigator, the injection site, along with the reason why the site was changed, should be recorded in the source documents and eCRF for each such occurrence.

Further details on IP administration are provided in the IP Handling Instructions. IP administration must be carried out according to these instructions.

After IP administration

Subjects will have had a pre-assessment (i.e., vital signs and lung function) prior to IP administration. For the first 4 doses of investigational product, subjects will be monitored after IP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later. For the fifth and subsequent doses of IP, subjects will be monitored after IP administration for a minimum of 1 hour with vital signs taken every 30 minutes or until stable, whichever is later.

Conditions requiring IP administration rescheduling

If any of the following should occur, the Investigator should reschedule the visit and IP should not be administered until the rescheduled visit:

- The subject has an intercurrent illness, that in the opinion of the Investigator may compromise the safety of the subject in the study (e.g., viral illnesses)
- The subject, in the opinion of the Investigator, is experiencing an acute or emerging asthma exacerbation
- The subject is febrile (defined as $\geq 38^{\circ}\text{C}$; $\geq 100.4^{\circ}\text{F}$) within 72 hours prior to IP administration

7.3 Labelling

Labelling of the IP will be carried out by AstraZeneca or designee in accordance with Annex 13 and current GMP and regulatory requirements of each country participating in the study. The labels will be translated into local languages where applicable and required by local regulations.

7.4 Storage

Tralokinumab/placebo is to be stored at the study site in a secured facility with limited access and controlled temperature. The temperature should be monitored on daily basis and documented in the temperature monitoring log.

The IP must be kept in the original outer container and under conditions specified on the label.

In the following cases:

- Temperature excursion upon receipt or during storage at the study site
- Damaged kit upon receipt, or
- Damaged syringe/cartridge,

site staff should not use the affected IP, and should immediately contact their AstraZeneca representative for further guidance. Damaged IP should be documented via IWRS/IVRS (please refer to the IWRS/IVRS manual for further details).

7.5 Compliance

The date and time of all IP administrations, as well as any missed doses, should be recorded in the appropriate section of the eCRF.

7.6 Accountability

The study drugs provided for this study will be used only as directed in the protocol.

It is the Investigator's responsibility to ensure that a procedure is established and maintained for the operation of the unblinded study drugs, this includes but is not limited to:

- The study drugs are administered only by a qualified, unblinded health professional named in the delegation of responsibility log.
- An unblinded health professional will account for all study drugs dispensed to the subjects.

An unblinded health professional, if applicable, or the blinded AstraZeneca monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery and destruction should be signed.

In case of malfunctioning APFS, the centre should contact the unblinded AstraZeneca monitor to initiate a product complaint process according to applicable guidelines.

7.7 Concomitant and other treatments

7.7.1 Concomitant medications

Information about any treatment in the 3 months prior to the date of the subject's informed consent or assent, and all the concomitant treatments given during the study, with reason for the treatment, will be collected by the Investigator/authorized delegate at each visit (as shown in [Table 1](#)) and recorded in the eCRF.

Note: to satisfy inclusion criterion [6](#), the history of continuous treatment with ICS corresponding to $\geq 500\mu\text{g}$ fluticasone propionate dry powder formulation equivalents plus a LABA for at least 3 months prior to Visit 1 should be documented in source and recorded in the eCRF (see section [4.1.1](#)).

Maintenance of asthma controller medication

All subjects are required to be treated with a stable dose of ICS corresponding to ≥ 500 µg fluticasone propionate dry powder formulation equivalents (as outlined in [Appendix F](#)) and LABA for at least 3 months prior to Visit 1 and during the treatment period. Subjects may also receive other physician prescribed asthma controller medications.

The aim of this study is to establish the treatment effect of tralokinumab as an add-on treatment and therefore the maintenance asthma controller therapy should be maintained at a stable dose from Visit 1 until the end of the treatment period, in order to prevent any independent confounding of the anticipated treatment effect of tralokinumab. **Changes to the subject's maintenance asthma controller medication regimen are discouraged during the treatment period**, unless judged medically necessary by the Investigator. Ideally, such changes should be discussed with the AstraZeneca Study Team Physician, prior to any change being made. All changes in the subject's maintenance medication should be documented in source along with rationale for change and recorded in eCRF.

Maintenance medication is not regarded as an IP, but will be provided/reimbursed by AstraZeneca according to local regulations, in order to maintain appropriate oversight and access to this concomitant therapy.

Please note that subjects on maintenance treatment with theophylline should have documented blood concentration levels within therapeutic range. If this is not documented before signing the informed consent, it can be obtained after informed consent has been given or as part of the Visit 1 procedures. The sample can be analysed at the central or local lab as applicable.

Rescue medication

Salbutamol, albuterol, or levalbuterol will be used as rescue medication during the study in the event of a worsening of asthma symptoms. As with the maintenance ICS-LABA, rescue medication is not regarded as an IP, but will be provided/reimbursed by AstraZeneca according to local regulations, in order to ensure access to essential rescue therapy.

7.7.2 Restrictions during and after the study

7.7.2.1 Asthma medication restrictions

Use of short-acting β_2 -agonists (SABA)

Regularly scheduled SABA use in the absence of any asthma symptoms is discouraged from enrolment and throughout the study duration. Prophylactic use of SABA (e.g., prior to planned exercise) if deemed necessary by the subject and the Investigator, may be used, but should **not** be recorded in the Asthma Daily Diary. Any such use should be documented in medical notes and recorded in the eCRF.

SABA via a metered dose device is permitted as needed for worsening asthma symptoms (i.e., rescue use) and will be recorded in the Asthma Daily Diary as number of inhalations.

Rescue use of SABA administered via jet or ultrasonic nebulization is allowed. Occasions where SABA was administered via nebulization will be recorded separately from metered dose inhaler inhalations in the Asthma Daily Diary.

Use of short acting anticholinergics

The use of short acting anticholinergics (e.g., ipratropium) as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event is not allowed from enrollment and throughout the study duration.

Use of long-acting β 2-agonists (LABA) as a reliever

The use of LABA as a reliever (e.g., Symbicort maintenance and reliever treatment) is not allowed from enrollment and throughout the study duration.

Use of once daily bronchodilators and theophylline

Use of theophylline and once daily BDs is allowed at the discretion of the Investigator. These drugs should have been used at a stable dose for at least 3 months before visit 1. A 48 hour minimum wash-out period for theophylline or once-daily BDs is required before spirometry. Should the subject be taking theophylline or the once daily BD in the evening, it is advised that the Investigator ask the subject to reschedule their theophylline or BD regimen to morning use, if there are no medical reasons to prevent this change.

Asthma medication restrictions on the days of scheduled site visit spirometry

Pre- and/or post-dose spirometry assessments will be performed at the study site at scheduled visits (see [Table 1](#)). Restriction to a subject's maintenance medication is required prior to the spirometry as described below (also see section [5.1.2](#)):

Visits 2 and 3

Subjects will be asked to withhold their twice daily BD therapy (including ICS-LABA) on the morning of the screening FEV₁ measurement and reversibility test for 12–24 hours prior to the assessment for eligibility (see Section [3.1](#), inclusion criteria [8](#) and [9](#)). For once daily BDs the required washout time is ≥ 48 hours. In case the subject does not meet the reversibility eligibility criteria, and a second re-test is done (not earlier than next calendar day and not later than 7 calendar days after the failed attempt), twice daily BDs may be withheld for 24 hours. In addition, SABA should not be used within 6 hours of these spirometry assessments. The subject's usual asthma medications may be administered following completion of the screening lung function procedures.

Treatment Period (Visits 4-29)

It is important that a true pre-BD (i.e., trough) FEV₁ reading obtained in order to maintain the integrity of planned efficacy analyses around lung function improvement. **Therefore, subjects will be asked to withhold their usual long acting BD and SABA as outlined in the section above for Visits 2 and 3.** The subject's usual asthma controller medications may be administered, following completion of the pre-BD spirometry. The suggested order of

administration of the subject's usual asthma controller, per protocol SABA (on visits where post-BD spirometry is assessed), and IP administration relative to scheduled pre and post-BD spirometry is given in section 5.1.2.

If the subject has taken their usual ICS-LABA and/or any other BD without an appropriate washout period (see Visits 2 and 3 above) before a site visit, the Investigator/authorized delegate should remind the subject of the importance of withholding their BD for an appropriate time and reschedule the visit for another day, within the allowed window.

If the subject has taken rescue SABA within 6 hours of the planned site visit spirometry they should ideally 1) remain at the site until such time that the 6 hour window has been reached or 2) return on another day, within the visit window. If neither of these options is feasible for the subject, spirometry may be performed with a notation indicating that the pre-BD spirometry was conducted within 6 hours of SABA use.

Asthma medication restrictions prior to home PEF testing

Subjects should avoid taking their morning asthma controller medication prior to the morning home PEF testing, and should conduct the evening home lung function testing before taking evening asthma controller medication. When possible, home PEF testing, should be taken at least 6 hours after the last dose of SABA reliever medication

Asthma medication restrictions on unscheduled visits

Asthma medication restrictions on unscheduled visits may not be feasible, and may be applied at the discretion of the Investigator. Timing of recent controller and reliever SABA use relative to the unscheduled spirometry should be noted in the record.

Asthma medication restrictions at site visits with scheduled dECG assessment

Subjects should be instructed not to take their usual asthma controller medication prior to scheduled dECG assessment. Use of SABA should be avoided within 6 hours prior to the dECG assessment.

The medication restriction is waived for the enrolment dECG at Visit 1.

7.7.2.2 Other medication restrictions

- Use of oral or systemic immunosuppressive medication is not allowed. Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator. Please see section 3.2, exclusion criteria 14 and 17 for examples and further details.
- Receipt of live attenuated vaccines within 30 days prior to randomization and during the study, including the follow up period, is not allowed. Inactive/killed vaccines (e.g., inactive influenza vaccine) are allowed provided they are not administered within 5 days before/after any dosing visit.

- Subject should not receive allergen immunotherapy injection on the same day as the IP administration
- Subjects should not take any other excluded medications:
 - oral or ophthalmic non-selective β -adrenergic antagonist (e.g., propranolol)
 - five-lipoxygenase inhibitors (e.g. Zileuton) or roflumilast

A table with medication-related restrictions is presented in [Appendix H](#).

7.7.2.3 Bronchial thermoplasty

Subjects must not undergo bronchial thermoplasty during the entire study.

7.7.3 Other treatments

Other treatments, which are considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator. If any such treatment includes medications other than those described above, these medications are to be recorded in the appropriate section of the eCRF.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

The main objectives of this study are to show efficacy in two tralokinumab dosing regimens vs. placebo with regards to asthma exacerbations (primary) and asthma symptom control (key secondary). If not otherwise stated, efficacy and safety analyses will be made versus the pooled placebo cohorts.

With regards to the key secondary objectives around asthma symptom control; to show increased asthma symptom control for tralokinumab vs. placebo the following is considered necessary:

- a) a significant effect in percent change from baseline in pre-dose/pre-BD FEV₁ at Week 52 vs. placebo **and**
- b) either a significant effect in mean change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary) at Week 52 **or** a significant mean change from baseline in Standardised AQLQ(S) +12 Total score at Week 52.

Asthma symptom control for a dosing regimen is only to be considered when a significant effect with regards to annualised asthma exacerbation rate up to Week 52 has been shown.

Significant results in both the key secondary outcome variables for FEV₁ and ACQ-6 could provide additional support for increased asthma symptom control.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first subject randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data. Analyses will be performed by AstraZeneca or its representatives.

All personnel involved with the analysis of the study will remain blinded until the database is locked and all protocol violations are identified.

8.2 Sample size estimate

A total study sample of 1,140 subjects are considered sufficient to show a reduction in AAER for the 2 dosing regimens of tralokinumab, compared to the pooled placebo cohorts (380 subjects on each active dosing regimen, 190 subjects into each of the Q2W and Q4W placebo regimens).

The sample size calculations are made in terms of subject years at risk and are based on an assumed exacerbation rate in the placebo group of 0.8, and shape parameter of 0.95 (over-dispersion). The methodology used is described in [Keene et al 2007](#) and the sample size is calculated for two-sided superiority tests at a significance level of 5% to achieve a power of 90%.

Assuming a uniform loss to follow-up of 15% during the study 380 randomized subjects per group is expected to provide approximately 350 subject-years at risk per treatment group. This is expected to provide at least 90% power for treatment effects down to 32% AERR.

8.3 Definitions of analysis sets

All efficacy analyses will be performed using an ITT approach based on the full analysis set. For consistency, demographic and baseline characteristics will be presented using the full analysis set. Safety objectives will be analyzed based on the Safety population.

All subjects analysis set (All subjects): This analysis set comprises all subjects screened for the study and will be used for the reporting of disposition and screening failures.

8.3.1 Efficacy analysis set

Full analysis set: All subjects randomized and receiving any IP will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Subjects will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued. For subjects who withdraw consent or assent to participate in the study all data will be included up to the date of their study termination.

8.3.2 Safety analysis set

Safety analysis set (Safety): All subjects who received any IP will be included in the safety analysis set. Subjects will be classified according to the treatment they actually received. A subject who has on one, or several occasions, received active treatment will be classified as active. If a subject has received both active dosing regimens (in error), then the subject will be

classified as having received the Q2W dosing regimen. All safety summaries will be based on this analysis set.

8.3.3 PK analysis set

Pharmacokinetic analysis set (PK): All subjects in the full analysis set who received tralokinumab; including PK blood samples that are assumed not to be affected by factors such as protocol deviations (e.g., disallowed medication, or incorrect study medication received). All PK summaries will be based on this analysis set.

8.3.4 PRO analysis set

PRO outcome variables will be evaluated based on the full analysis set.

8.4 Outcome measures for analyses

8.4.1 General Definitions

8.4.1.1 Definition of baseline and subject baseline variables

For spirometry variables the measurement recorded at the baseline visit (Visit 3) will be used as baseline. If the Visit 3 measurement is missing, the last non-missing value before Visit 3 will be used as baseline instead. For post-BD FEV₁, the measurement after the first BD administration is the baseline.

The baseline for the ePRO variables (ACQ-6, AQLQ(s)+12, WPAI-CIQ, and EQ-5D-5L) will be captured on the ePRO device at Visit 3. Baseline for Asthma Daily Diary variables will be the bi-weekly mean for data collected between study day -14 and -1 (i.e. 14 to 1 day before Visit 3).

For laboratory data and physical examination, baseline will be defined as the latest non-missing assessment prior to first dose.

Absolute change from baseline outcome variables is computed as (post-randomization value – baseline value).

Percent change from baseline is computed as ((post-randomization value – baseline value) / baseline value) × 100%. If either the post-randomization value or the baseline value is missing, then the absolute or percent change from baseline value will also be set to missing.

8.4.1.2 Visit and period windows

For the exacerbation-related analyses no windows will be applied.

For the patient reported questionnaires collected in the ePRO, the variables will be summarized based on the protocol scheduled Days with ± 3-day window.

For the other questionnaires, the window is the same as the protocol-defined visit windows. For local laboratory data, and all vital signs, the visit recorded in the WBDC system will be used.

For the central laboratory results and other endpoints that present visit-based data, the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows.

A more detailed definition of visit and period windows will be provided in the statistical analysis plan.

8.4.2 Calculation or derivation of efficacy variables

8.4.2.1 Exacerbation rate

The primary endpoint is the annualised asthma exacerbation rate (AAER) up to Week 52.

In the statistical analysis, the number of asthma exacerbations experienced by a subject during the 52-week double-blind treatment period will be used as response variable, and the logarithm of the subject's corresponding follow-up time will be used as an offset in the analysis to adjust for subjects having different exposure times during which the events occur. Asthma exacerbation is defined in Section 5.1.1

In order to calculate the number of exacerbations experienced by a subject during the 52-week treatment period the following rule will be applied:

- The start of an exacerbation is defined as the start date of systemic corticosteroids, ER or urgent care visits requiring systemic corticosteroids, or hospital admissions due to asthma, whichever occurs earlier, and the end date is defined as the last day of systemic corticosteroids, ER or urgent care visit, or hospital discharge, whichever occurs later.

Additional systemic corticosteroid treatments, ER or urgent care visits requiring use of systemic corticosteroids, or inpatient hospitalization due to asthma occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled.

Maximum follow-up time for a subject is approximately 52 weeks; defined as the time from randomization to the date of Visit 29. For a subject lost to follow-up, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed.

For the production of summary statistics, the annual asthma exacerbation rate per subject is calculated, and standardized per a 52-week period according to the formula described below.

*Annual Exacerbation Rate = No. of Exacerbations * 365.25 / (Follow-up date – Visit 3 date + 1).*

8.4.2.2 Proportion of subjects with ≥ 1 asthma exacerbation during 52 weeks of treatment

The proportion of subjects with ≥ 1 asthma exacerbation during the 52 weeks of treatment will be a supportive variable to the primary objective. The variable will categorize each subject as having at least one asthma exacerbation or not (yes/no).

8.4.2.3 Time to first exacerbation

Time from randomization to the first asthma exacerbation will also be used as a supportive variable to the primary objective, and is calculated as follows:

$$\text{Start Date of first asthma exacerbation} - \text{Date of Randomization} + 1.$$

The time to first asthma exacerbation for subjects who do not experience an asthma exacerbation during the treatment period will be censored at the date of their last visit for the 52-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed.

8.4.2.4 Forced expiratory volume in 1 second

The key secondary variable is the pre-dose/pre BD FEV₁

The percent change from baseline to each of the post-randomization visits (post Visit 3), up to and including the end of 52-week double-blind treatment visit (Visit 29), will be used as secondary efficacy outcome variable.

The absolute change from baseline to each of the post-randomization visits (post Visit 3) up to and including the end of 52-week double-blind treatment visit (Visit 29) will be used as a supportive outcome variable.

The same outcome variables will be derived for the secondary variable pre-dose/post- BD FEV₁.

8.4.2.5 Forced Vital Capacity and Forced Expiratory Flow at 25-75%

The percent change from baseline to each of the post-randomization visits, up to and including the end of 52-week double-blind treatment visit (Visit 29) will be calculated for the exploratory variables FVC and FEF_{25-75%}.

8.4.2.6 Annualised asthma exacerbation rate associated with an ER or urgent care visit or a hospitalization

The AAER associated with an ER or urgent care visit or a hospitalization will be a secondary efficacy variable.

The number of asthma exacerbations that are associated with an ER or urgent care visit or a hospitalization experienced by a subject during the 52-week treatment period will be derived according to the following rule:

The start date of an asthma-related ER or urgent care visit or hospitalization is the start date of the ER or urgent care visit or hospitalization.

The cessation date of an asthma-related ER or urgent care visit or hospitalization is the stop date of the ER or urgent care visit or hospitalization.

In the statistical analysis, the number of asthma exacerbations that are associated with an ER or urgent care visit or a hospitalization experienced by a subject during the 52-week double-blind treatment period will be used as response variable, and the logarithm of the subject's corresponding follow-up time will be used as an offset in the analysis to adjust for subjects having different exposure times during which the events occur.

Maximum follow-up time is approximately 52 weeks, and the follow-up time is derived as described in Section [8.4.2.1](#)

Additionally, for the production of descriptive statistics, the annualised rate of asthma-related ER or urgent care visits and hospitalizations will be calculated using the same methodology as the annualised rate of exacerbations described in Section [8.4.2.1](#).

8.4.3 Calculation or derivation of patient reported outcome variables

Patient-reported outcomes data will be captured via an ePRO device. The definition of key secondary and secondary outcome variables are provided in the following sections.

8.4.3.1 Asthma symptom score

Asthma symptoms during night-time and daytime will be recorded by the subject each morning and evening in the Asthma Daily Diary. Symptoms will be recorded using a scale 0-3, where 0 indicates no asthma symptoms. Asthma symptom daytime score, night-time score, and total score will be calculated separately.

The total daily symptom score will be calculated by taking the sum of the daytime and night-time asthma symptom scores for each day. If a subject is missing a value for either daytime or night-time asthma symptom score on a given day then the total score for that day will be set to missing.

The key secondary outcome variable is the biweekly mean daily asthma symptom total score. The daily asthma symptom total score is defined as the sum of the daytime and night-time symptom scores as captured in the Asthma Daily Diary. The biweekly mean is calculated as the mean daily asthma symptom total over 14 sequential days. If more than 7 daily scores (>50%) within that period is missing, then the daily asthma symptom mean score is set to 'missing'.

8.4.3.2 Rescue medication use

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the subject in the Asthma Daily Diary twice daily.

The number of inhalations of rescue medication captured in the eDiary each day will be calculated per subject. If a subject is missing a value for either morning or evening rescue medication on a given day, then the total rescue medication use for that day will be set to missing.

Total rescue medication use, defined as the average number of inhalations (puffs) per day will be calculated as the outcome variable.

8.4.3.3 Home peak expiratory flow (morning and evening)

Changes from baseline in morning and evening PEF up to Week 52 will be calculated.

8.4.3.4 Asthma Control Questionnaire (ACQ-6)

In the ACQ-6 questionnaire the subjects are asked to recall the status of their asthma during the previous week with regards to symptom and use of short acting β -agonists. The questionnaire include questions on

- a) Awoken at night by symptoms
- b) Limitation of normal daily activities
- c) Waking in the morning with symptoms
- d) Dyspnoea
- e) Wheeze
- f) Daily rescue medication

The questions of the ACQ-6 are measured on a 7-point scale scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-6 score is computed as the un-weighted mean of the responses.

Other variables based on ACQ-6 to report include:

- ACQ-6-responder (Yes=1/No=0)
 - Responder: Change from baseline ACQ-6 score ≤ -0.5
 - Non-responder : Change from baseline ACQ-6 score > -0.5
- ACQ-6-responder (improved/No Change / Deterioration)
 - Improvement: Change from baseline ACQ-6 score ≤ -0.5
 - No change: $-0.5 < \text{Change from baseline ACQ-6 score} < 0.5$
 - Deterioration: Change from baseline ACQ-6 score ≥ 0.5
- Subjects asthma control as measured by ACQ-6 score:
 - Well controlled : ACQ-6 score ≤ 0.75
 - Partly controlled : $0.75 < \text{ACQ-6 score} < 1.5$

- Not well controlled : ACQ-6 score ≥ 1.5

8.4.3.5 Asthma quality of life questionnaire for 12 years and older (AQLQ(S) +12)

The AQLQ(S)+12) will be first completed at Visit 3 (Week 0), which will be used as the baseline assessment. Subjects are asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment).

The overall score is calculated as the mean response to all questions. The 4 individual domain scores (4 domains assessing 1) symptoms, 2) activity limitations, 3) emotional function, and 4) environmental stimuli) are the means of the responses to the questions in each of the domains.

The key outcome variable for the AQLQ(S)+12 will be the change in mean score from baseline to each of the post-randomization periods. The change from baseline will be derived as post-randomization score minus baseline score, there will be no imputation for missing values.

Other variables based on AQLQ(S) +12 to be reported include:

- AQLQ(S) +12 -responder (Yes=1/No=0)
 - Responder: Change from baseline AQLQ(S) +12 score ≥ 0.5
 - Non-responder : Change from baseline AQLQ(S) +12 score < 0.5
- AQLQ(S) +12 -responder (improved/No Change / Deterioration)
 - Improvement: Change from baseline AQLQ(S) +12 score ≥ 0.5
 - No change: $-0.5 < \text{Change from baseline AQLQ(S) +12 score} < 0.5$
 - Deterioration: Change from baseline AQLQ(S) +12 score ≤ -0.5

8.4.3.6 European quality of life-5 dimensions-5 levels (EQ-5D-5L)

The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty.

The subject will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the subject will be asked to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state.

The change from baseline in visual analogue scale will be calculated by visit.

8.4.3.7 Health care resource utilization

Broad-based health care utilization event information will be collected by the Investigator/authorized delegate at each visit as specified in the protocol and recorded in the appropriate eCRF module. Examples include aspects such as unscheduled physician visits or telephone calls or ambulance transport.

8.4.3.8 The Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ)

The Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ) will be first completed at visit 3 (Week 0), which will be used as the baseline assessment.

The WPAI+CIQ questionnaire is a 10-item questionnaire that assesses productivity and activity impairment over the previous week.

There are a maximum of 10 questions and a minimum of 3 questions that will be completed by subjects as follows:

- a) Currently employed (yes/no)
- b) Hours missed work due to health problems
- c) Hours missed work due to other reasons
- d) Hours actually worked
- e) Degree health affected productivity while working (0-10 scale, with 0 meaning no effect)
- f) Attends class in an academic setting (yes/no)
- g) Hours missed class due to health problems
- h) Hours actually attended class
- i) Degree health affected productivity while attending class (0-10 scale, with 0 meaning no effect)
- j) Degree health affected regular activities (other than work or class) (0-10 scale, with 0 meaning no effect)

If the answer to question 1 is 'No, not currently employed', then the subject should skip to question 6. If the answer to question 6 is 'No, not currently attending class', then the subject should skip to question 10.

The WPAI+CIQ provide 4 scores:

- Absenteeism (work or class time missed),
- Presenteeism (impairment at work or class/reduced on-the-job effectiveness),

- Work productivity loss (overall work or class impairment/absenteeism plus presenteeism)
- Activity impairment.

WPAI+CIQ outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

For the work related questions, the following calculations should be used to create the outcomes of interest:

- Absenteeism = $Q2/(Q2+Q4)$
- Presenteeism = $Q5/10$
- Work Productivity Loss = $Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4)) \times (Q5/10)]$
- Activity Impairment = $Q10/10$

The class related questions will be used in a similar manner

8.4.4 Calculation or derivation of safety variable(s)

The following safety data will be collected: vital signs, physical examination, 12-lead dECG, hematology, clinical chemistry, urinalysis, and reported AEs.

Change from baseline (Visit 3) to each post-baseline time point where scheduled assessments were made will be calculated for relevant measurements.

8.4.4.1 Adverse events

Adverse events experienced by the subjects will be collected throughout the entire study and will be coded by the AstraZeneca designee using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

AE data will be categorized according to their onset date into the following study periods:

- AEs occurring during run-in (onset date \geq visit 1 and before the first dose of study treatment)
- AEs occurring during treatment (onset date \geq the first day of study treatment and \leq the last day of study treatment + dosing frequency)
- AEs occurring during follow-up, consisting of AE with
 - onset date $>$ the last day of study treatment + dosing frequency and \leq date of week 56; this is only applicable for subjects that are treated for the entire treatment period
 - onset date $>$ the last day of study treatment + dosing frequency and \leq the last day of study treatment + dosing frequency + 4 weeks ; this is only applicable for subjects that prematurely discontinued treatment

- AEs occurring post-treatment (onset date > the last day of study treatment + dosing frequency + 4 weeks; this is only applicable for subjects that prematurely discontinued treatment)

Note: Here the ‘dosing frequency’ equals to 2 weeks for subjects randomized to the 2QW dosing regimen, and to 4 weeks for subjects randomized to the 4QW dosing regimen.

8.4.4.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or discontinuations due to AEs.

Based on the expert’s judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that led to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

8.4.4.3 Laboratory variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times detailed in the CSP, and will be assessed in a central laboratory. The parameters outlined in [Table 2](#), [Table 3](#), [Table 4](#) and [Table 5](#) in [Section 5.1.6.1](#), will be collected. Laboratory data will be reported in SI units.

Changes in haematology and clinical chemistry variables between baseline and each subsequent scheduled assessment will be calculated. Baseline is defined as the last available value measured prior to the first dose of randomized treatment. The change from baseline is defined as the treatment period value minus the baseline period value. There will be no imputation for missing values.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The AstraZeneca extended reference ranges will be used for laboratory variables (where they exist). All values (absolute and change) falling outside the reference ranges will be flagged.

Urinalysis data will be categorised as negative (0), trace or positive (+) at each time-point.

For the purposes of haematology, clinical chemistry and urinalysis shift tables, baseline will be defined as the latest non-missing assessment prior to first dose, and on-treatment will be defined as the latest non-missing assessment whilst the subject is ongoing on treatment.

For the liver function tests: AST, ALT, ALP, GGT and total bilirubin, the multiple of the AstraZeneca ULN (not extended) range will be calculated for each data point.

$$\text{Multiple} = \text{Value} / \text{ULN}$$

i.e., if the ALT value was 72 IU/L (ULN 36) then the multiple would be 2.

Subjects who meet any of the following criteria at any point during the study will be flagged:

$$\text{Multiple} = \text{Value} / \text{ULN}$$

i.e., if the ALT value was 72 IU/L (ULN 36) then the multiple would be 2.

Subjects who meet any of the following criteria at any point during the study will be flagged:

- $\text{AST} \geq 3 \times \text{ULN}$
- $\text{ALT} \geq 3 \times \text{ULN}$
- $\text{TBL} \geq 2 \times \text{ULN}$

8.4.4.4 dECGs

Twelve-lead dECG measurements will be recorded in accordance with the protocol, with the baseline visit being defined as Visit 1.

The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

8.4.4.5 Physical examination

Complete and brief physical examinations will be performed at time points specified in [Table 1](#). What is included in the assessment will be dependent on whether the examination is complete or brief, as described in Section [5.1.7](#). For the brief physical examination, only information on whether the assessment was performed or not will be recorded.

Each component of the baseline visit (i.e., Visit 3) complete physical examination will be recorded as normal or abnormal. Each component of the follow-up complete physical examinations will be recorded as normal, same as baseline, or new/aggravated.

Any new finding(s), or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE.

8.4.4.6 Vital signs

Pre-dose vital signs (pulse, systolic blood pressure, diastolic blood pressure, respiration rate and body temperature) will be obtained in accordance with the schedule provided in [Table 1](#).

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated. Baseline will be defined as the last value prior to the first dose of randomized treatment. The change from baseline will be defined as the treatment period value minus the baseline period value. There will be no imputation for missing values.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Body mass index (BMI) will be calculated from the height (in meters) and weight (in kilograms) as follows:

$$\text{BMI} = \text{kg/m}^2$$

8.4.5 Calculations or derivation of Pharmacokinetic and Immunogenicity variables

Blood samples (processed to serum) for pharmacokinetic and immunogenicity assessments will be collected from all subjects at baseline prior to first IP administration at Visit 3, at multiple time points before IP administrations during the treatment period, and at selected timepoints in the follow-up phase of the study. Anti-drug antibodies assessments will be conducted utilizing a tiered approach (screen, confirm, titer). These validated methods are conducted using a bridging assay format and statistically determined floating screening assay cut point factor and confirmatory assay cut point. The minimal sample dilution is 1:13. Titer values are reported as the reciprocal of the highest dilution that yields a value above the cut point. Samples from pre-defined study time points that confirm positive for ADA will also be tested for neutralizing ADA (nAb) activity. Both ADA and nAb will be summarized using descriptive statistics as described in Section 8.5.9.

Pharmacokinetics and immunogenicity of tralokinumab:

Tralokinumab serum concentrations will be tabulated by time along with descriptive statistics. Population PK modelling may also be performed to better characterize the PK of tralokinumab, but will be reported separately from the CSR.

The incidence rate of ADA to tralokinumab will be reported by tralokinumab treatment group. If possible and if relevant, the impact of ADA occurrence on the PK and PD and safety will be summarized in the CSR.

8.5 Methods for statistical analyses

The main focus for the statistical analysis is to compare both dosing regimens of tralokinumab to placebo, with regards to the primary, key secondary, and safety objectives.

The analysis of the study endpoints will include all data captured during the 52-week double-blind treatment period. This includes data regardless of whether study treatment was prematurely discontinued or delayed, and/or irrespective of protocol adherence, unless the subject withdraws consent or assent to study participation.

Summary data will be presented in tabular format by treatment. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables for parametric data will be summarized by descriptive statistics including N, mean, SD,

median, and range. All data will be listed. Data listings will be sorted by treatment and subject number.

All hypothesis testing will be reported using 2-sided tests. P-values will be rounded to 3 decimal places.

8.5.1 Testing strategy for primary and key secondary objectives

The hierarchical testing strategy described below will be used for the primary and key secondary outcomes in the two dosing regimens. The described testing strategy will globally strongly control the Type I error (FWER).

Step 1:

The higher dosing regimen (300 mg tralokinumab Q2W) will be tested versus placebo at a two-sided 5% significance level with regards to the primary endpoint.

Step 2:

If a treatment effect is shown with regards to the primary endpoint for Q2W in Step 1, then

- a) the family of key secondary endpoints will be tested for Q2W at a two-sided 4% significance level using the hierarchical testing approach described further below.
- b) the primary endpoint will be tested for Q4W dosing regimen using a two-sided test at (at least) 1% significance level. Any significance level retained from the key secondary testing family for Q2W (bullet a) above) will be recycled to this test; hence, the significance level in this test depends on the results from testing the family of key secondary endpoints for Q2W, as follows:
 - Case 1: All key secondary endpoints exhibits significance for Q2W => primary endpoint will be tested for Q4W at level $\alpha=0.05$
 - Case 2: All key secondary endpoints within the family, except one endpoint in Level 2 (see below), exhibits significance for Q2W => primary endpoint will be tested for Q4W at level $\alpha=0.03$
 - Case 3: All other scenarios => primary endpoint will be tested for Q4W at level $\alpha=0.01$

Step 3:

If treatment effect is shown for the primary endpoint for Q4W in step 2, then the family of key secondary endpoints will be tested for Q4W at significance level α retained from Step 2, using the hierarchical testing approach described below.

Hierarchical testing approach for key secondary endpoints

In Step 2 and 3 the family of key secondary endpoints will be tested using the following hierarchical testing structure with strong local FWER control:

- **Level 1:** Percent change from baseline in pre-dose/pre-BD FEV₁ at Week 52 vs. placebo will be tested two-sided at significance level α retained from previous step. If significant treatment effect is shown, proceed to next level, else stop. All subsequent results within the family will be declared non-significant.
- **Level 2:** Mean change from baseline in bi-weekly mean daily asthma symptom score at Week 52 and mean change from baseline in AQLQ(S)+12 Total score at Week 52 will be tested using a Bonferroni approach at significance α . Hence, each of the endpoints will be tested two-sided at significance level $\alpha/2$ ($=0.02$ in the Q2W comparison, $=0.005$, 0.015 , or 0.025 in the Q4W comparison).

If significant treatment effect is shown in at least one of the endpoints in this level, proceed to Level 3, else stop. The subsequent result within the family will be declared non-significant and interpreted in a descriptive, exploratory way.

- **Level 3:** Change from baseline in ACQ-6 will only be tested if at least one of the endpoints in Level 2 exhibit significance. Hence, there can be two different outcomes in Level 2 resulting in testing the hypothesis for ACQ-6:
 - Case 1: Both comparisons in Level 2 exhibit significance \Rightarrow ACQ-6 is testable and will be tested at level α ($=0.04$ in the Q2W comparison, $=0.01$, 0.03 , or 0.05 in the Q4W comparison)
 - Case 2: Only one of the comparisons in Level 2 exhibit significance \Rightarrow ACQ-6 is testable and will be tested at level $\alpha/2$ ($=0.02$ in the Q2W comparison, $=0.005$, 0.015 , or 0.025 in the Q4W comparison).

8.5.2 Sensitivity analyses

The interpretation of exacerbation data post-discontinuation of treatment is likely to be confounded by reduced quality of objective confirmation of deterioration, and by the use of subsequent therapies. Sensitivity analyses for the primary endpoint will be carried out to explore the impact of this, e.g. exclusion of data post-discontinuation of treatment.

Sensitivity analyses for the primary endpoint and the key secondary endpoints based on different missing data mechanism assumptions including those expected to be more conservative such as missing not at random will be used to explore the robustness of any treatment effect, including multiple imputation approaches. Full details of the sensitivity analyses will be pre-specified in SAP and documented prior to database lock of the studies.

8.5.3 Subject disposition, demography data and subjects characteristics

Subject disposition will be summarized using the All subjects analysis set.

The number of enrolled subjects will be summarized. The number and percentage of subjects within each treatment group will be presented by the following categories; randomized, not randomized (and reason), received study treatment, didn't receive study treatment (and reason), completed treatment, discontinued treatment (and reason), completed study, and discontinued study (including reason).

Demographic data such as age, gender, and race will be summarized by treatment group for the full analysis set.

Various baseline characteristics will also be summarized by treatment for the full analysis set. These include medical, surgical and respiratory disease histories, weight, height and BMI, smoking status, history of allergy, FEV₁ (pre and post-BD) at baseline, asthma duration, age at onset of asthma, asthma medications, the number of asthma exacerbations in the previous 12 months, and the number of asthma exacerbations requiring hospitalizations in the previous 12 months.

Medical and surgical histories will be summarized by MedDRA Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA.

The number and percentage of subjects who take concomitant medications, and those who take disallowed concomitant medications during the study, will be presented by treatment group. Concomitant medications will be classified according to the AstraZeneca Drug Dictionary. The summary tables will present data by generic term using Anatomical Therapeutic Chemical (ATC) classification system codes.

8.5.4 Exposure

Exposure to IP will be summarized by treatment group, for the safety analysis set.

8.5.5 Violations and deviations

Only important protocol deviations will be listed and tabulated in the CSR. Protocol deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being include:

- Subjects who do not meet the inclusion criteria
- Subjects who do not meet the randomization criteria
- Subjects who meet any of the exclusion criteria
- Subjects who use one or more disallowed medication (for any reason, unless otherwise specified) during the randomized treatment period
- Subjects who received the incorrect study treatment or study dose at any time during the 52-week double-blind treatment period
- Subjects who developed withdrawal criteria during the study but were not withdrawn

8.5.6 Analysis of the primary variable

The primary efficacy variable is the AAER and the primary analysis is to compare the AAER for tralokinumab with placebo.

For each dosing regimen the primary objective will be evaluated through the hypothesis test:

H_0 : rate ratio (tralokinumab/placebo) equals 1 vs.

H_1 : rate ratio does not equal 1.

The AAER in the tralokinumab group will be compared to that seen in the placebo group using a negative binomial model. The response variable in the model will be the number of asthma exacerbations experienced by a subject, over the 52-week double-blind treatment period. Covariates and factors included in the model will include at least treatment and the stratifying variables. The logarithm of the subject's corresponding follow-up time will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events occur.

The standard parameterization approach (NB2) of the Negative model will be applied ([Hilbe 2011](#)).

The estimated treatment effect (i.e., the rate ratio of tralokinumab versus placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the rate ratio will be presented. In addition, the AAER and the corresponding 95% CI within each treatment group will be presented.

The individual exacerbation criteria (ER or urgent care visits due to asthma that required systemic corticosteroids, hospitalization due to asthma, or use of systemic corticosteroids) will also be summarized descriptively.

8.5.7 Analysis of secondary variable(s)

All efficacy secondary objectives will be analyzed based on the full analyze population.

8.5.7.1 Lung Function

The key secondary outcome variable for lung function is: *Percent change from baseline in pre-dose/pre-BD FEV₁*

The percent change from baseline in pre-dose/pre-BD FEV₁ at Week 52 will be compared between tralokinumab and placebo using a repeated measures analysis on all subjects with a baseline pre-dose/pre-BD FEV₁ measurement in the full analysis set.

The dependent variable will be the percent change from baseline in pre-BD FEV₁ at post-baseline protocol-specified visits (up to the EOT visit). Treatment group and the variables used in the stratified randomization will be included as independent variables. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be

unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

Percent change in FEV1 = Treatment group + stratifying variables + visit + treatment*visit

Results will be presented in terms of LSMEANS, treatment differences in LSMEANS, 95% confidence intervals and p-values. Summary statistics of the change from baseline for all visits in the FEV₁ at study site will be produced by treatment group.

8.5.7.2 Asthma symptoms

The key secondary outcome variable: Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily).

The change from baseline in asthma symptom total score, daytime score, and night-time score at Week 52 will each be summarized and analyzed using the repeated measurement approach defined for change from baseline in pre-dose/pre-BD FEV₁, as described in Section 8.4.2.4. Included in the model will also be the baseline mean daily asthma symptom score.

8.5.7.3 Asthma specific health-related quality of life

The key secondary outcome variable: Change from baseline in AQLQ(s)+12 total score.

The change in mean score from baseline for AQLQ(S)+12 at Week 52 will be summarized and analyzed using the repeated measurement approach defined for change from baseline in pre-dose/pre-BD FEV₁, as described in Section 8.4.2.4. Included in the model will also be the baseline AQLQ(s)+12 total score.

Supportive outcome variable: AQLQ(S)+12 responder (yes/no)

Responder variables AQLQ(S)+12 (yes/no) will be analyzed using a logistic regression model with covariates of at least treatment, stratifying variables, and baseline value.

The number and percentage of subjects with AQLQ(s)+12 total score changes ≥ 0.5 will be summarize by treatment (identified as a large meaningful change). Additionally, the number and percentage of subjects achieving an improvement, no change, or deterioration will be summarized by treatment as per Section 8.4.3.5.

Supportive outcome variable: change from baseline to overall post-baseline mean of AQLQ(S)+12.

8.5.7.4 ACQ-6 defined asthma control

The key outcome variable: Change from baseline in ACQ-6

Change in mean score from baseline for ACQ-6 will be summarized and analyzed using the repeated measurement approach defined for change from baseline in pre-dose/pre-BD FEV₁,

as described in Section 8.4.2.4. Included in the model will also be the baseline ACQ-6 mean score.

Supportive outcome variable: ACQ-6 responder (yes/no).

Responder variables ACQ-6 (yes/no) will be analyzed using a logistic regression model with covariates of at least treatment, stratifying variables, and baseline value.

The number and percentage of subjects achieving mean $ACQ-6 \leq 0.75$, $0.75 < \text{mean } ACQ-6 < 1.5$ and mean $ACQ-6 \geq 1.5$ at EOT will be summarized by treatment. Additionally, the number and percentage of subjects achieving an improvement, no change, or deterioration as per Section 8.4.3.4, ACQ-6 will also be summarized by treatment.

Supportive outcome variable: change from baseline to overall post-baseline mean of ACQ-6.

8.5.7.5 Biomarker positive population based on subject's baseline periostin or baseline DPP4 values

A structured exploration of the relationship between outcome, biomarkers and treatment group will be performed to evaluate the potential prognostic and predictive value of biomarkers, in order to identify a biomarker positive subpopulation which will be further evaluated in study D2210C00008 to confirm the effect of tralokinumab on the primary and key secondary endpoints in this population. The relative and absolute benefit of treatment in relation to the size of the potential subpopulation will be considered in selecting the final biomarker positive subpopulation. The focus will be on the Q2W treatment regimen compared to placebo, with baseline periostin as the primary biomarker of interest, but also considering baseline DPP4 values that may be associated with up regulation of IL-13.

The following sequential steps will be taken, with further details of each step to be specified in the statistical analysis plan:

- A parametric model will be established for the relationship between exacerbation rate and baseline periostin by treatment group as follows:
 - Exacerbation rate will be analysed, with a negative binomial model including covariates of geographical region, number of exacerbations in the year before the study, baseline periostin value, treatment group (with the two placebo regimens pooled), and interaction between periostin value and treatment group.
 - Non-parametric smoothed estimates of the relationship between exacerbation rate baseline periostin by treatment group will be produced. This will also be repeated for key secondary endpoints.
 - The fit of the parametric model will be assessed in comparison to the observed data and to the non-parametric smoothed estimates. If the fit is considered inadequate then alternatives will be considered, initially using a log

transformation of baseline periostin value, and then other simple monotonic transformations if necessary.

- The selected parametric model will be used to produce estimates of the relationship between exacerbation rate and baseline periostin by treatment group which will be used to inform the selection of a periostin cut-off to define a biomarker positive subpopulation. Cross-validation will be used to minimise bias due to over-fitting. The selection will be primarily based on the primary endpoint in the Q2W tralokinumab dosing regimen and the pooled placebo regimens. Consideration will be given to the key secondary endpoints if these can further contribute to the choice of an appropriate cut-point.
- The steps above will be repeated using baseline DPP4 in place of periostin to assess whether it provides a marked improvement over periostin to identify the final biomarker positive subpopulation.
- The selected parametric model will be used to assess the utility of the selected biomarker using a continuous interaction test.

The final biomarker positive subpopulation will then be further studied in study D2210C00008 to confirm the effect of tralokinumab on the primary and key secondary endpoints in this population.

8.5.7.6 Other endpoints associated with asthma exacerbations

Proportion of subjects with ≥ 1 asthma exacerbation

The proportion of subjects with ≥ 1 asthma exacerbation during the 52 weeks of treatment will be addressed as a supportive variable to the primary objective. The proportion of subjects in the active tralokinumab arm will be compared with the proportion in the placebo group in both populations using a Cochran–Mantel–Haenszel test controlled for stratifying variables.

The results of the analyses will be presented as weighted difference in the proportion of subjects who have ≥ 1 asthma exacerbation, together with associated 95% CI and 2-sided p-value for each active dose regimen versus placebo. The number and percentage of subjects with ≥ 1 asthma exacerbation will also be summarized by randomized treatment for both populations.

Time to first asthma exacerbation

Time to first asthma exacerbation will be analyzed as another supportive efficacy variable to the primary objective to explore the extent to which treatment with tralokinumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with including treatment and at least stratifying variables as covariates.

Results of the analysis will be summarized as hazard ratios, 95% confidence intervals and p-values.

Time to first asthma exacerbation will be displayed graphically using a Kaplan-Meier plot. The median time to event will be summarized by randomized treatment, if there is sufficient uncensored data available to calculate these median values. The percentage of subjects who are exacerbation free at 22 and 44 Weeks will be estimated for each treatment group.

8.5.7.7 Emergency room or urgent care visits and hospitalizations due to asthma

Annual rate of asthma exacerbations that are associated with an ER or urgent care visit or a hospitalization will be analyzed using a similar Negative binomial model as outlined for the primary efficacy variable in Section 8.5.6.

8.5.7.8 Health care resource utilization and productivity loss due to asthma

WPAI-CIQ

The WPAI+CIQ data will be summarized by treatment as described in Section 8.4.3.8, including the 4 types of scores: absenteeism, presenteeism, work/class productivity loss, and activity impairment described. The number and percentage of subjects with asthma specific resource utilization (defined in Section 8.4.3.8) will be presented by treatment group.

8.5.7.9 Asthma symptom, general health-related quality of life and asthma control

This section specifies analyses addressing the secondary objectives other than the key secondary objectives described in Sections 8.5.7.2, 8.5.7.3, and 8.5.7.4.

Nights with awakening due to asthma

The number of nights with awakening due to asthma and requiring rescue medication will be summarized and analyzed in the same way as rescue medication use, below.

Rescue medication use

Total rescue medication use (average puffs/day) will be analyzed as the response variable by fitting a linear model to the data. Treatment group will be fitted as the explanatory variable, and at least stratifying variables will be fitted as covariates. The results will be presented in terms of LSMEANS, difference between treatments in LSMEANS, and 95%CI. The number and percentage of subjects within each treatment group who received rescue medication will be summarized by visit.

Home PEF (morning and evening)

Change from baseline in morning and evening PEF at Week 52 will each be summarized and analyzed using a similar model as the model for change from baseline in pre dose/pre-BD FEV₁, as described in Section 8.5.7.1

European quality of life-5 dimensions-5 levels (EQ-5D-5L)

The EQ-5D-5L responses from each dimension and the visual analogue scale (VAS) will be summarized by treatment group and period. Shift tables will be produced for each dimension, and the change from baseline in VAS will be summarized with descriptive statistics by visit.

8.5.8 Safety and tolerability

All safety variables will be summarized using the safety analysis set and data presented according to treatment received.

8.5.8.1 Adverse events

AEs will be summarized separately for the treatment and follow-up periods, as defined in Section 6.3. AEs occurring during the run-in period, or occurring post-treatment (as per the definition above) will be listed, but not summarized.

An overall summary table will be produced showing the number and percentage of subjects with at least 1 AE in any of the following categories; AEs, SAEs, deaths due to AE, DAEs, and other significant adverse events (OAEs). The total number of AEs in the different AE categories in terms of AE counts will also be presented (i.e., accounting for multiple occurrences of the same event in a subject).

AEs will be summarized by SOC and PT assigned to the event using MedDRA. For each PT, the number and percentage of subjects reporting at least one occurrence will be presented i.e., for a subject multiple occurrences of an AE will only be counted once.

AEs (by PT) will be summarized by causality and maximum intensity. If a subject reports multiple occurrences of the same AE, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe). SAEs, OAEs, DAEs, and deaths will also be summarized in separate tables.

The rate of AEs per person-years at risk, calculated as (number of subjects reporting AE)/(total time at risk of AE), will also be reported. Rates will typically be expressed in terms of events per 100 subject-years.

Separate listings of subjects with AEs, SAEs, death due to AE, or discontinuations due to AEs will be presented.

8.5.8.2 Laboratory data

All continuous laboratory parameters will be summarized by absolute value at each visit by treatment group, together with the corresponding changes from baseline. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD. Mean changes from baseline over time will also be plotted by treatment group.

AstraZeneca defined extended reference ranges will be used for the identification of individual clinically important abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, high, and missing values. The shift tables will

present baseline and maximum/minimum on-treatment value, as applicable for each parameter.

Shift plots showing each individual subject's laboratory value at baseline and at maximum/minimum will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points then shift plots of these data may be produced. A diagonal line indicating no change, and horizontal and vertical reference lines indicating the limits of the AstraZeneca defined reference ranges will also be displayed on the shift plots.

Data for subjects who have treatment-emergent changes outside the predefined criteria will be presented. This data presentation will include all visits for this subset of subjects.

The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (using AstraZeneca defined reference ranges) occurring during the clinical study will also be given.

In order to identify potential Hy's Law cases, maximum post baseline total bilirubin will be plotted against maximum post baseline ALT, expressed as multiples of ULN. This plot will be repeated to show maximum post baseline total bilirubin against maximum post baseline AST, expressed as multiples of ULN. These plots will be produced on a log scale and reference lines will be included at 2xULN for total bilirubin and at 3xULN for ALT/AST.

For all subjects who meet the biochemical criteria for Hy's law (potential Hy's Law), a Subject Safety Narrative will be produced, and the relevant laboratory parameters will be tabulated showing all visits for these subjects. Subjects with elevated ALT or AST, and elevated total bilirubin, at any time may be explored further graphically using individual subject profile plots.

For urinalysis data, a shift table will be generated to present changes from baseline to EOT. The number of subjects with treatment-emergent changes will also be summarized. Here, treatment-emergent changes are defined as None/Trace at baseline to Positive, at any visit after baseline.

Any data outside the AstraZeneca normal and extended reference ranges will be explicitly noted on the listings that are produced.

8.5.8.3 dECGs

The Investigator's assessment of the 12-lead dECG (normal or abnormal) will be listed for all subjects, along with detailing whether any abnormalities were clinically significant or not.

The number and percentage of subjects with clinically significant abnormal dECGs will be summarized by treatment group and visit.

8.5.8.4 Physical Examination

Shift tables (normal, abnormal) of baseline versus EOT will be generated, presenting the assessment for each component of the complete physical examination separately.

Listings of abnormal results will be produced.

8.5.8.5 Vital Signs

Vital signs data will be presented in the same way as described in [Section 8.5.8.2](#) for the clinical laboratory data, and will be presented using AstraZeneca defined reference ranges, and clinically important change criteria.

All recorded vital signs data will be listed.

8.5.8.6 Analysis of Immunogenicity variables

ADA status (positive vs. negative) at each visit will be summarized by treatment group. Descriptive statistics including number of subjects, mean, standard deviation, median, and range of the actual ADA titers by treatment group and visit, where possible, will be provided. The ADA status across the study for each subject (positive vs. negative) will also be classified and summarized by treatment group. The association of ADA status across the study (positive vs. negative) with AEs/SAEs may be evaluated. In addition, the association of ADA titers (\geq median titer in positive subjects vs. $<$ median titer) with AE/SAEs may be evaluated for ADA-positive treated subjects only. The ADA-positive subjects across the study may also be divided into persistent positive versus transient positive. A subject will be considered as persistent positive if he/she has positive ADAs for at least two consecutive visits. Otherwise, the subject will be considered as transient ADA positive. The associations between ADA and AE/SAEs may be summarized for both persistent positive subjects versus transient positives subjects.

Neutralizing antibody evaluations will be conducted on those serum samples that test positive for ADA at end of treatment and also during the study follow up period. The test sample is deemed positive or negative for the presence of nAb to tralokinumab relative to a pre-determined (in assay validation), statistically derived cut point. Samples positive for nAb to tralokinumab are then titered to determine relative amounts of nAb present in each test sample.

For ADA, all subjects with titer information will be shown in the data listing.

8.5.9 Analysis of pharmacokinetics

All analyses of pharmacokinetics variables will be based on the PK data set, all analyses on Immunogenicity variables will be based on the safety analysis set.

Due to the limited sampling schedule, the PK assessment will be primarily based on the observed steady-state serum trough (pre-dose) concentrations, C_{trough} . Empirical evaluation of potential impact of demographic covariates and ADA on C_{trough} will be conducted.

The PK data will be merged with those from other clinical studies for a population-based meta-analysis. Results of the meta-analysis will be presented in a separate pharmacometrics report outside of the CSR.

8.5.10 Interim analysis

No interim analysis is planned for this study.

A blinded sample size re-estimation will be performed before last subject enrolled in the study. The analysis will be performed by AstraZeneca or its representatives. A detailed description on this will be included in the statistical analysis plan.

8.5.11 Exploratory analysis

The analysis of exploratory objectives will be specified in the statistical analysis plan.

8.5.11.1 Baseline periostin and DPP4 levels as predictive biomarkers

The utility of subject's baseline periostin level and DPP4 levels as predictive continuous biomarkers for treatment effect on asthma exacerbation rate and asthma symptom control will be explored. A detailed description of the planned explanatory analyses will be given in the statistical analysis plan.

8.5.11.2 Deoxyribonucleic acid collected for future exploratory research

Results relating to the exploratory objective "To collect and store DNA for future exploratory research into genes/genetic variation that may influence clinical response to tralokinumab and provide information on phenotypes of severe asthma (optional)" will be reported outside of the CSR.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational site staff, and also train them on any study specific procedures, the WBDC and IVR/IWR systems, ePRO and ePEF devices, spirometers, and any other system(s) that may be utilised in the study.

The Principal Investigator will ensure that appropriate training relevant to the study is provided to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will ensure that a record of all individuals involved in the study (medical, nursing and other staff) is maintained.

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contact with the study site, including site visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational site team is adhering to the protocol, data are being accurately and timely recorded in the CRFs, biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent or assent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic/hospital charts)
- Ensure withdrawal of informed consent or assent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the Investigator(s) or other personnel at the site require information and advice about the study conduct.

9.2.1 Source data

Please refer to the Clinical Study Agreement (CSA) for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the site should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects. In all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator should follow the principles and terms outlined in the CSA pertaining to the archival of study documents.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in Q2, 2014 and to end by Q3, 2017.

The study may be terminated at individual sites if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with tralokinumab.

9.4 Data management by AstraZeneca

Data management will be performed by the AstraZeneca Data Management Centre according to the Data Management Plan (DMP). Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The DMP will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

Data will be entered in the WBDC system at the study site.

Site personnel will be trained on use of the WBDC system and will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system. eCRF Instructions will be provided to the personnel at the study site as guidance for performing data entry. Data entered in the WBDC system will be immediately saved to a central database and all changes will be tracked in the system's audit trail. All data will be Source Data Verified (SDV) by an AstraZeneca site monitor (or representative), reviewed /queried and updated as needed.

Data queries will be raised for inconsistent, impossible, or missing data, and must be resolved in a timely manner. Clean file occurs when all data have been declared clean and signed off by all investigators. Data will be frozen and then locked to prevent further data entry/editing. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRFs will be provided to and archived at the study site when the study has been locked.

Data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports will be produced and reconciled with the Subject Safety database and/or the investigational site.

Data Management of genotype data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Genotype data will be transferred to the clinical database, and merged with the clinical data from the main study, prior to the statistical analysis and reporting of the study.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

Management of external data

Data Management will determine the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (as applicable).

Data Management will ensure that the data collection tool (e.g., ePRO diary, IVRS/IWRS, etc.) will be tested/validated as necessary. External data reconciliation will be done with the clinical database as applicable.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent or assent Form(s) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.2.1 Pharmacogenomic data

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Precautions will be taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a

medical emergency, an AstraZeneca Physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An Ethics Committee (EC)/Institutional Review Board (IRB) should approve the final study protocol, including the final version of the subject's ICF (and assent form for subjects under the age of majority), and any other written information and/or materials to be provided to a subject. The Investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The EC/IRB should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the ICF (and/or assent form for subjects under the age of majority) that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the ICF (and assent form for subjects under the age of majority), should be approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, ECs/IRBs and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent and assent

The Principal Investigator(s) at each site will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time

- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent (and assent form for subjects under the age of majority) before conducting any procedure specifically for the study
- Ensure the original, signed ICFs (and assent form for subjects under the age of majority) are stored in the Investigator's Study File
- Ensure copies of the signed ICFs (and assent form for subjects under the age of majority) are given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent or assent form that is approved by an Ethics Committee.

10.5 Changes to the protocol and informed consent or assent forms

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant EC/IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to ECs/IRB, see Section [10.3](#).

If a protocol amendment requires a change to a site's ICF (and/or assent form for subjects under the age of majority), AstraZeneca and the site's EC/IRB are to approve the revised ICF (and/or assent form for subjects under the age of majority) before the revised form(s) is/are used.

If local regulations require, any administrative change will be communicated to or approved by each EC/IRB.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and

any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the site.

11. LIST OF REFERENCES

Accordini et al 2006

Accordini S, Bugiani M, Arossa W, Gerzeli S, Marinoni A, Olivieri M, et al. Poor control increases the economic cost of asthma. A multicentre population-based study. *Int Arch Allergy Immunol.* 2006;141(2):189-98. Epub 2006 Aug 4.

Bateman et al 2010

Bateman ED, Reddel HK, Eriksson G, Peterson S, O'stlund O, Sears MR, Jenkins C, MD, Humbert M, Buhl R, Harrison TW, Quirce S, and. O'Byrne PM. Overall asthma control: The relationship between current control and future risk. *American Academy of Allergy, Asthma & Immunology* doi:10.1016/j.jaci.2009.11.033. 2010; 125(3); 600-08.

Dweik et al 2011

Dweik RA et al. An official ATS clinical practical guideline: Interpretation of exhaled nitric oxide levels (FE_{NO}) for clinical applications. *Am. J. Respir. Crit. Care Med.* 2011;184:602-615.

GINA 2012

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) December 2012. Available from: URL:
<http://www.ginasthma.org/guidelinesginareport-global-strategy-for-asthma.html>.

Grunstein et al 2002

Grunstein MM, Hakonarson H, Leiter J, Chen M, Whelan R, Grunstein JS, Chuang S. IL-13-dependent autocrine signaling mediates altered responsiveness of IgE sensitized airway smooth muscle. *Am J Physiol Lung Cell Mol Physiol.* 2002;282:L520-8.

Hallett et al 2012

Hallett MA, Venmar KT, Fingleton B. Cytokine stimulation of epithelial cancer cells: the similar and divergent functions of IL-4 and IL-13. *Cancer Res.* 2012 Dec 15;72(24):6338-43. Epub 2012 Dec 7.

Hershey 2003

Hershey GK. IL-13 receptors and signaling pathways: an evolving web. *J Allergy Clin Immunol.* 2003;111(4):677-90.

Hilbe 2011

Hilbe J. M. (2011) "Negative Binomial Regression" Cambridge University Press ISBN: 978-0521-19815-8.

Juniper et al 2006

Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006; 100: 616- 621.

Keene et al 2007

Keene ON, Jones MRK, Lane PW, et al. Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study. *Pharm Stat* 2007;6:89–97.

Lieberman et al 2010

Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol.* 2010 Sep;126(3):477-80.e1-42.

Miller et al 2005

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J.* 2005 Aug;26(2):319-38.

Piper et al 2013

Piper E, Brightling C, Niven R, Oh C, Faggioni R, Poon K, et al. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J.* 2013;41(2):330-8.

Quanjer et al 2012

Quanjer PH, Stanojevic S, Cole TJ, Baur X, L Hall GL, Culver B, Enright PL, Hankinson JL, Zheng J, Stocks J and the ERS Global Lung Function Initiative. Multi ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations.. Report of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved Lung Function Reference Values. 2012 Jun, as doi: 10.1183/09031936.00080312.

Reddel et al 2009

Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al on behalf of the American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations: Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. *Am. J. Respir. Crit. Care Med.* 2009;180:59-99.

Sampson et al 2006

H.A. Sampson, A. Munoz-Furlong, R.L. Campbell, N.F. Adkinson Jr., S.A. Bock, A. Branum *et al.* Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*, 117 (2006), pp. 391–397.

Sorkness et al 2008

Sorkness RL, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF, Curran-Everett D, Erzurum SC, Gaston BM, Israel E, Jarjour NN, Moore WC, Peters SP, Teague WG, Wenzel SE. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation. *J Appl Physiol* 104: 394–403, 2008.

Tamhane et al 2008

Tamhane AC, Liu L. On weighted Hochberg procedures. *Biometrika* 2008; 95: 279–294.

Wardlaw et al 1988

Wardlaw AJ, Dunnette S, Gleich GJ, Collins JV, Kay AB. Eosinophils and mast cells in bronchoalveolar lavage in subjects with mild asthma. Relationship to bronchial hyperreactivity. *Am Rev Respir Dis.* 1988; 137:62-9.

Wenzel 2012

Wenzel S E. Asthma phenotypes: the evolution from clinical to molecular approaches. 2012 May 4, 18(5):716-25.

Wills-Karp et al 1998

Wills-Karp M, Luyimbazi J, Xu X, Schofield B, Neben TY, Karp CL, et al. Interleukin-13: central mediator of allergic asthma. *Science.* 1998;282(5397):2258-61.



Clinical Study Protocol Appendix B

Drug Substance Tralokinumab (CAT-354)

Study Code D2210C00007

Edition Number 1.0

Date

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

‘Life-threatening’ means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a “reasonable possibility” that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.



Clinical Study Protocol Appendix C

Drug Substance Tralokinumab (CAT-354)

Study Code D2210C00007

Edition Number 1.0

Date

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance
Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Clinical Study Protocol Appendix D	
Drug Substance	Tralokinumab (CAT-354)
Study Code	D2210C00007
Edition Number	1.0
Date	

Appendix D
Pharmacogenetics Research

TABLE OF CONTENTS	PAGE
TABLE OF CONTENTS.....	1
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	3
1. BACKGROUND AND RATIONALE.....	4
2. GENETIC RESEARCH OBJECTIVES	4
3. GENETIC RESEARCH PLAN AND PROCEDURES	4
3.1 Selection of genetic research population	4
3.1.1 Study selection record.....	4
3.1.2 Inclusion criteria	4
3.1.3 Exclusion criteria	5
3.1.4 Discontinuation of subjects from this genetic research	5
3.2 Collection of samples for genetic research	5
3.3 Coding and storage of DNA samples.....	5
4. ETHICAL AND REGULATORY REQUIREMENTS.....	6
4.1 Informed consent	6
4.2 Subject data protection.....	6

5.	DATA MANAGEMENT.....	6
6.	STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE	7
7.	LIST OF REFERENCES (NOT APPLICABLE).....	7

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event
CSP	Clinical Study Protocol
DNA	Deoxyribonucleic acid
LIMS	Laboratory Information Management System

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the tralokinumab clinical development programme to explore how genetic variations may affect the clinical parameters associated with tralokinumab. Collection of deoxyribonucleic acid (DNA) samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to tralokinumab, but also susceptibility to asthma for which tralokinumab may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to asthma.

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence the clinical response (ie, distribution, safety, tolerability and efficacy) to tralokinumab.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol (CSP) **and**:

- Provision of signed and dated written informed consent for pharmacogenetic sampling and analyses. If a subject declines to participate in the pharmacogenetic research, there will be no consequence or loss of benefit to the subject. The subject will not be excluded from the other aspects of the study described in this CSP, as long as they consent to participate in the main study

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection

3.1.4 Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in [Section 3.10](#) of the main CSP.

3.2 Collection of samples for genetic research

The blood sample for genetic research will ideally be obtained from the subject at Visit 1, but may be taken at any later visit if Visit 1 is not suitable. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. Only 1 sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For the volume of blood to be drawn from each subject for this sample, see [Table 6](#) in Section 5.1.6 of the main CSP.

3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of the Last Subject Last Visit after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory personnel working with the DNA).

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in [Section 10](#) of the main CSP.

4.1 Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the informed consent form for the main study and the genetic component of the study. Copies of both the signed and dated written informed consent forms must be given to the subject and the original filed at the study centre. The Principal Investigators are responsible for ensuring that consent is given freely and that the subjects understand that they may freely discontinue from the genetic aspect of the study at any time.

4.2 Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory Authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the Clinical Study Report for the main study, or in a separate report as appropriate.

Genotype data will be transferred to the clinical database, and merged with the clinical data from the main study, prior to the statistical analysis and reporting of the study.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

7. LIST OF REFERENCES (NOT APPLICABLE)

Clinical Study Protocol Appendix E

Drug Substance	Tralokinumab (CAT-354)
Study Code	D2210C00007
Edition Number	1.0
Date	

Appendix E

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

	TABLE OF CONTENTS	PAGE
	TABLE OF CONTENTS.....	2
1.	INTRODUCTION	3
2.	DEFINITIONS.....	3
3.	IDENTIFICATION OF POTENTIAL HY’S LAW CASES.....	3
4.	FOLLOW-UP	4
4.1	Potential Hy’s Law Criteria not met	4
4.2	Potential Hy’s Law Criteria met	4
5.	REVIEW AND ASSESSMENT OF POTENTIAL HY’S LAW CASES.....	5
6.	REFERENCES	6

1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) $\geq 3x$ Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) $\geq 2x$ ULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT $\geq 3x$ ULN **and** TBL $\geq 2x$ ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT $\geq 3x$ ULN
- AST $\geq 3x$ ULN
- TBL $\geq 2x$ ULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:
- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician

- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
 - The 'Medically Important' serious criterion should be used if no other serious criteria apply
 - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) ‘Drug-induced liver injury: Premarketing clinical evaluation’:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

Clinical Study Protocol Appendix F

Drug Substance	Tralokinumab (CAT-354)
Study Code	D2210C00007
Edition Number	2.0
Date	

Appendix F

Maintenance Therapy Equivalence Table

Estimated daily doses for inhaled corticosteroids.

Asthma Therapy Inhaled Corticosteroid	Total Daily Dose (µg/day)	
	Medium ¹	High
Beclomethasone dipropionate	>500 - 1000	>1000 - 2000
Beclomethasone HFA	>240 - 480	>480
Beclomethasone dipropionate (Fostair)	>200 - 400	>400 - 800
Ciclesonide	>160 - 320	>320 - 1280
Triamcinolone acetonide	>1000 - 2000	>2000
Flunisolide	>1000 - 2000	>2000
Fluticasone furoate	100	200
Fluticasone propionate	>250 - 500	>500 - 1000
Fluticasone propionate HFA	>364 - 440	>440
Budesonide	>400 to 800	>800 - 1600
Budesonide, if as delivered dose (eg Symbicort)	>320 to 640	>640 - 1280
Mometasone furoate	≥ 400	≥800

¹ The acceptable medium ICS dose for this study is bolded.

Clinical Study Protocol Appendix G

Drug Substance	Tralokinumab (CAT-354)
Study Code	D2210C000007
Edition Number	1.0
Date	

Appendix G

Anaphylaxis: definition criteria, signs and symptoms, and management

1. INTRODUCTION

As with any antibody, allergic reactions to dose administration are possible. The World Health Organization has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic [IgE-mediated and non-IgE-mediated (e.g., IgG and immune complex mediated) and nonimmunologic (Johansson et al, 2004)]. The clinical criteria for defining anaphylaxis for this study are listed in section 2. A guide to the signs and symptoms and management of acute anaphylaxis is provided in section 3. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample will be drawn from the patient as soon as possible after the event, at 60 minutes \pm 30 minutes after the event, and at discharge for analysis of serum tryptase.

2. CLINICAL CRITERIA FOR DEFINING ANAPHYLAXIS AND IMMUNE COMPLEX DISEASE

Anaphylaxis

In adults, anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:
 - (a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
 - (b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - (a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
 - (b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

- (c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence).
 - (d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that patient's baseline.

Immune Complex Disease

Immune complex disease or Hypersensitivity Type III is evoked by the deposition of antigen-antibody or antigen-antibody-complement complexes on cell surfaces, with subsequent involvement of breakdown products of complement, platelets, and polymorphonuclear leukocytes, and development of vasculitis; serum sickness and nephritis is common.

3. SIGNS AND SYMPTOMS AND MANAGEMENT OF ACUTE ANAPHYLAXIS

Anaphylaxis is an acute and potentially lethal multi-system allergic reaction in which some or all of the following signs and symptoms occur:

- Diffuse erythema
- Pruritus
- Urticaria and/or angioedema
- Bronchospasm
- Laryngeal edema
- Hypotension
- Cardiac arrhythmias
- Feeling of impending doom
- Unconsciousness
- Shock

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhea

- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps and bloating
- Lightheadedness
- Headache
- Uterine cramps
- Generalized warmth

4. MANAGEMENT OF ACUTE ANAPHYLAXIS

4.1 Immediate intervention

1. Assessment of airway, breathing, circulation, and adequacy of mentation
2. Administer epinephrine intramuscularly every 5-15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock and unconsciousness.

4.2 Possibly appropriate, subsequent measures depending on response to epinephrine

- (a) Place patient in recumbent position and elevate lower extremities.
- (b) Establish and maintain airway.
- (c) Administer oxygen.
- (d) Establish venous access.
- (e) Normal saline IV for fluid replacement.

4.3 Specific measures to consider after epinephrine injections, where appropriate

- (a) Consider epinephrine infusion.
- (b) Consider H1 and H2 antihistamines.
- (c) Consider nebulized β_2 agonist [e.g., albuterol (salbutamol)] for bronchospasm resistant to epinephrine.
- (d) Consider systemic corticosteroids.

- (e) Consider vasopressor (e.g. dopamine).
- (f) Consider glucagon for patient taking b-blocker.
- (g) Consider atropine for symptomatic bradycardia.
- (h) Consider transportation to an emergency department or an intensive care facility.
- (i) For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

Adapted from: Kemp SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 2008; 63(8):1061-70.

Clinical Study Protocol Appendix H

Drug Substance Tralokinumab (CAT-354)

Study Code D2210C00007

Edition Number 2.0

Date

Appendix H
Restricted and prohibited medications

PROHIBITED AND RESTRICTED MEDICATIONS

Asthma medication restrictions

Table 1 Asthma medication restrictions

Medication	Prohibited/restricted	Details
Maintenance treatment with long-acting bronchodilators (including ICS-LABA)	Restricted	<p>Changes in dose and regimen should not be done from enrolment and throughout the study treatment (unless there is a medical need as judged by the Investigator)</p> <p>Usual ICS-LABA should not be taken prior to scheduled spirometry, ECG and home lung function assessments (to be administered once assessments are completed)</p> <p>Subjects should be instructed not to use their twice daily bronchodilators within 12 hours of the scheduled site visit spirometry. For once daily bronchodilators a 48 hour washout period is required. Subjects will not need to washout of their asthma medications for unscheduled visits due to asthma worsening.</p>
Short acting beta-agonists (SABA)	Restricted	<p>Regular scheduled use not allowed from enrolment through the study duration.</p> <p>Rescue use of SABA administered via nebulisation is discouraged, except as urgent treatment during an asthma exacerbation.</p> <p>SABA should not be used within 6 hours prior to scheduled site visit spirometry, ECG and home lung function assessments with the exception of any unscheduled visits due to asthma worsening.</p>

Additional Maintenance Controllers	Allowed with restriction	<p>Stable dose for 3 months prior to Visit 1; stable dose during the treatment period</p> <p>Subjects on theophylline should have blood concentration levels within therapeutic range documented before Visit 1.</p> <p>Subjects should be instructed not to use additional once daily bronchodilators within 48 hours of the scheduled spirometry at site visits, with the exception of any unscheduled visits due to asthma worsening</p>
Short acting anticholinergics (e.g. ipratropium)	Restricted	<p>Not allowed from enrollment and throughout the study as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event</p> <p>May be used for managing an asthma exacerbation event.</p>
Long-acting beta-agonists as a reliever (e.g. Symbicort Maintenance and Reliever Treatment)	Prohibited	Not allowed from enrolment and throughout the study duration
Zileuton	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period

Other medication restrictions

Table 2 Other medication restrictions

Medication	Prohibited/restricted	Details
Live Attenuated Vaccines	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period and 4 months (5 half-lives) after the last dose of the investigational product
Inactive/killed vaccinations	Restricted	Allowed provided they are not administered within 5 days before or

Medication	Prohibited/restricted	Details
(e.g. inactive influenza)		after any study visit
Any immunomodulators or immunosuppressives	Prohibited	Not allowed 3 Months or 5 Half Lives (whichever is longer) prior to Visit 1; during treatment period; 3 Months or 5 Half Lives (whichever is longer) after Last Dose
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF; during treatment period
Any marketed (e.g. omalizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1; during treatment period; 4 months or 5 half-lives (whichever is longer) after the last dose of the investigational product
Other investigational Products (including investigational use of an approved drug)	Prohibited	Not allowed 30 Days or 5 Half Lives (whichever is longer) prior to Visit 1; during treatment period
Allergen Immunotherapy	Restricted	Allowed if on stable therapy for at least 30 days prior to date of ICF; no anticipated changed during treatment period
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period
Roflumilast	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period
Oral or ophthalmic non-selective β -adrenergic antagonist (e.g. propranolol)	Prohibited	Subjects currently using any oral or ophthalmic non-selective β -adrenergic antagonist at the time of enrolment are not eligible for the study. Not allowed during treatment period.

Medication	Prohibited/restricted	Details
Medications not currently licensed for use in the treatment of asthma, for example medications for Chronic Obstructive Pulmonary Disease, and not part of current standard of care	Prohibited	Not allowed 30 days prior to Visit 1. Not allowed throughout the duration of the study.